SURVEY AND SUMMARY

The diverse superfamily of lysine acetyltransferases and their roles in leukemia and other diseases

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ABSTRACT

Acetylation of the ε-amino group of lysine residues, or Nε-lysine acetylation, is an important post-translational modification known to occur in histones, transcription factors and other proteins. Since 1995, dozens of proteins have been discovered to possess intrinsic lysine acetyltransferase activity. Although most of these enzymes were first identified as histone acetyltransferases and then tested for activities towards other proteins, acetyltransferases only modifying non-histone proteins have also been identified. Lysine acetyltransferases form different groups, three of which are Gcn5/PCAF, p300/CBP and MYST proteins. While members of the former two groups mainly function as transcriptional co-activators, emerging evidence suggests that MYST proteins, such as Esa1, Sas2, MOF, TIP60, MOZ and MORF, have diverse roles in various nuclear processes. Aberrant lysine acetylation has been implicated in oncogenesis. The genes for p300, CBP, MOZ and MORF are rearranged in recurrent leukemia-associated chromosomal abnormalities. Consistent with their roles in leukemogenesis, these acetyltransferases interact with Runx1 (or AML1), one of the most frequent targets of chromosomal translocations in leukemia. Therefore, the diverse superfamily of lysine acetyltransferases executes an acetylation program that is important for different cellular processes and perturbation of such a program may cause the development of cancer and other diseases.

INTRODUCTION

The question of how protein functions are regulated *in vivo* has been and remains a central issue in studies of various biological processes. Acetylation of the ε-amino group of lysine residues, or Nε-lysine acetylation, has recently emerged as an important covalent post-translational modification for regulating protein functions (1–7). Lysine acetylation has been mainly found in eukaryotic cells, but more recently also in archaea and eubacteria (8–11). This type of modification ought to be distinguished from acetylation of the α-amino groups of N-terminal residues, or Nα-terminal acetylation, which occurs in many eukaryotic proteins (12). Nα-terminal acetylation mainly occurs in a co-translational manner and is generally irreversible (12), whereas lysine acetylation is a reversible post-translational process. The dynamic equilibrium of lysine acetylation *in vivo* is governed by the opposing actions of acetyltransferases and deacetylases. The very first direct links of histone acetyltransferase (HAT) and histone deacetylase to transcriptional co-regulators, made in 1996 (13,14), initiated a gold rush to identify proteins with such enzymatic activities. It is now clear that there are three major classes of histone deacetylases (15–19). In comparison, proteins with HAT activity are more diverse (4,6,20–22). Some known HATs also actetylate other proteins (20,23). Using different protein substrates, several proteins have recently been found to possess intrinsic lysine acetyltransferase activity (24–27). Interestingly, at least two of them are unable to acetylate histones. Since acetyltransferases modifying non-histone proteins have begun to emerge, the generic term 'lysine acetyltransferases (LATs)' is used hereafter to refer to enzymes that are able to acetylate specific lysine residues within histones and/or other proteins. In what follows, I will first list various types of proteins modified by lysine acetylation and present an overview of different groups of LATs, with a special focus on the MYST family of acetyltransferases to illustrate how similar catalytic domains are used for different functional purposes in various eukaryotic organisms. I will then discuss how activities of LATs are regulated, what determines their substrate specificity and how lysine acetylation affects protein function. Evidence for the involvement of aberrant HATs in human leukemia will be described at the end, to conclude that LATs are potential molecular targets for therapeutic intervention of leukemia and other diseases caused by abnormal lysine acetylation.

LYSINE ACETYLATION IN DIFFERENT TYPES OF PROTEIN

The occurrence of acetyllysine in histones was first discovered in the 1960s (28–30). Core histone proteins were found to be

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Table 1. Types of protein known to be modified by lysine acetylation

Type of protein	Functional consequence of acetylation
Core histone	
H2A	Chromatin loosening/gene activation
H2B	Chromatin loosening/gene activation
H3	Chromatin loosening/gene activation
H4	Chromatin loosening/gene activation, histone deposition/nucleosome assembly
Non-histone chromatin protein	
HMG14 and HMG17	Inhibit nucleosome binding
DNA-binding transcription factor	
p53, ELKF, HMGI(Y), TCF, NF-κB, MyoD, GATA1, E2F1, HNF4 and ~30 others	Alter DNA binding, co-regulator interaction, ubiquitination, stability and nuclear localization
Transcriptional co-regulator	
ATCR	Inhibit coactivator association
CIITA	Nuclear accumulation andubiquitination
β-Catenin	c-Myc gene activation
RB	Inhibit phosphorylation and increase MDM2 association
RIP140	Block CtBP association
General transcription factor	
TFIIE	Not determined
TFIIF	Not determined
TFIIB	Stimulate TFIIF association and transcriptional activation
HAT autoacetylation	
PCAF	Promote nuclear localization
p300, CBP, MOZ, MORF, etc.	Not determined
Chromatin remodeler	
Brm	Block transcriptional activation and growth inhibition
DNA replication factor	
MCM3	Inhibit DNA replication
Chromatid cohesion protein	
Cohesin subunits	Not determined
DNA metabolic enzyme	
Flap endonuclease-1	Inhibit DNA binding and nuclease activity
Thymine DNA glycosylase	Block interaction with the repair endonuclease APE
Werner DNA helicase	Augment translocation into nuclear foci
Signaling regulator	
Smad7	Prevent ubiquitination and proteasomal degradation
Cytoskeletal protein	
α-Tubulin	Increase cell motility
Nucleocytoplasmic trafficking protein	
Importin α	Not determined
Viral protein	
HIV Tat	Regulate RNA binding, co-regulator interaction and transcriptional activation
Adenoviral E1A	Inhibit CtBP association and stimulate nuclear accumulation
Large T antigen	Stimulate DNA replication
Archaeal chromatin protein	
Alba	Inhibit oligomerization and DNA binding
Bacterial protein	
Acetyl-CoA synthetase	Inhibit enzymatic activity
CheY	Regulate the chemotaxis response

acetylated at the ε-amino nitrogen of specific lysine residues located in the N-terminal tails (reviewed in 31). Importantly, histone acetylation appeared to be associated with active chromatin (28). In 1979, lysine acetylation of high mobility group (HMG) proteins was observed (32). In 1987, Lys40 of α-tubulin from *Chlamydomonas* was identified as the acetylation site (33). A decade later, in 1997, the tumor suppressor protein p53 was discovered to be acetylated at specific lysine residues in its C-terminal regulatory domain (34). Together with the finding that HATs acetylate the general transcription factors TFIIE and TFIIF *in vitro* (35), the unexpected discovery of p53 acetylation revealed that HATs are also able to acetylate non-histone proteins, thereby unleashing numerous studies aimed at assessing lysine acetylation in various proteins. It is well recognized now that this type of modification occurs much more widely than

anticipated several years ago. As listed in Table 1, over 30 DNA-binding transcription factors have been found to be N^ε-acetylated (20,23,36). At least five transcriptional co-regulators are known to be similarly modified (37–41). Reminiscent of autophosphorylation found with protein kinases, several HATs are autoacetylated (42–45). Autoacetylation of PCAF (p300/CBP-associated factor) is important for nuclear localization (46) and acetylation of the general transcription factor TFIIB by itself promotes TFIIF association and transcriptional activation (26). In addition, the chromatin remodeler Brm is acetylated at a lysine residue (47). Although most known N^ε-acetylated proteins are histones and transcriptional regulators (Table 1), this modification also occurs in other cellular proteins, including MCM3 (minichromosome maintenance 3) (24), DNA metabolic enzymes (48–50), the signaling regulator Smad7 (51) and α-tubulin (33). Just as in cellular proteins,

**Table 2.** Classification of known lysine acetyltransferases

Family	LAT	Organism	Substrate	Stoichiometric complex	Established roles/function
Hat1	Hat1	*S.cerevisiae* to mammals	H4	Hat B	Histone deposition, chromatin assembly and gene silencing
Gcn5/PCAF	Gcn5	*S.cerevisiae*	H4/H2B	SAGA, ADA, HAT-A2, SLIK/SALSA	Transcriptional co-activator
	PCAF	Mammals	H3/H4, TFs, E1A, TAT	PCAF	Transcriptional co-activator
	GCN5L	Worms to mammals	H3/H4, TFs[a]	STAGA, TFTC	Transcriptional co-activator
p300/CBP	CBP	*C.elegans* to mammals	Histones, TFs, E1A		Transcriptional co-activator
	p300	Mammals	Histones, TFs, E1A, TAT		Transcriptional co-activator and E4 ubiquitin ligase for p53
MYST	Sas2	*S.cerevisiae*	H4 K16[b]	SAS	Gene silencing
	Sas3	*S.cerevisiae*	H3	NuA3	Transcriptional elongation
	Esa1	*S.cerevisiae*	H4/H2A	NuA4, piccolo NuA4	Transcriptional coactivator and cell cycle control
	Mof	*Drosophila*	H4 K16	MSL	Gene dosage compensation
	Chameau	*Drosophila*			PcG-dependent gene silencing
	Enok	*Drosophila*			Neuroblast proliferation
	TIP60	Mammals	H3/H4, androgen receptor	TIP60	Transcriptional co-regulator, DNA repair and apoptosis
	MOF	Mammals	H4	MAF2	Transcriptional co-activator
	HBO1	Mammals	H3/H4[b]		DNA replication, transcriptional co-repressor
	MOZ	Mammals	H3/H4		Transcriptional co-activator
	MORF	Mammals	H3/H4		Transcriptional co-activator
p160	SRC-1	Mammals	H3/H4		Transcriptional co-activator
	ACTR	Mammals	H3/H4		Transcriptional co-activator
CIITA	CIITA	Mammals	H4		Transcriptional co-activator
ATF2	ATF2	Mammals	H4/H2B		Transcriptional activator
TAF$_{II}$250	TAF$_{II}$230	*Drosophila*	H3/H4	TFIID	Transcription initiation
	TAF$_{II}$250	Mammals	H3/H4	TFIID	Transcription initiation, kinase and ubiquitin ligase
TFIIIC	TFIIIC subunits	*S.cerevisiae* to mammals	H3/H4		Transcription initiation
Nut1	Nut1	*S.cerevisiae*	H3/H4	Mediator	Transcription initiation
Elp3	Elp3	*S.cerevisiae* to mammals	Histones	Elongator	Transcription elongation, lysine demethylase?
CDY	CDY	Humans	H4		
	CDYL	Mammals	H4		Histone-to-protamine transition during spermatogenesis
Hpa2	Hpa2	*S.cerevisiae*	H3/H4		Unknown
	Hpa3	*S.cerevisiae*			Unknown
TFIIB	TFIIB	*S.cerevisiae* to mammals	TFIIB		Transcription initiation
MCM3AP	MCM3AP	Mammals	MCM3		DNA replication initiation
Eco1	Eco1	Mammals	Cohesin subunits		Sister chromatid cohesion
ARD1	ARD1	Mammals	HIF1α		pVHL association, ubiquitination and degradation

[a]TF, transcription factor.
[b]Recombinant enzymes have weak activity, but their respective complexes are much more active.

N$^\varepsilon$-acetylation has been found in viral proteins, including the HIV TAR RNA-binding protein Tat, adenoviral oncoprotein E1A and polyomavirus large T antigen (52–55). Moreover, lysine acetylation is not just unique to eukaryotic and viral proteins. The archaeal architectural protein Alba is N$^\varepsilon$-acetylated and this modification blocks oligomerization and DNA binding (8,9). Acetylation of Lys609, a catalytic residue of acetyl-CoA synthetase from the enterobacterium *Salmonella enterica*, inhibits the enzymatic activity *in vivo* (10,11). This residue is invariant among a family of AMP-forming enzymes from prokaryotes and eukaryotes, so acetylation may modulate the function of these enzymes (10,11). More amazingly, acetylation of Lys92 dramatically up-regulates the function of *Escherichia coli* chemotaxis regulator CheY (56,57). Therefore, lysine acetylation has emerged as a general post-translational modification that regulates functions of various cellular and viral proteins.

DIFFERENT TYPES OF LYSINE ACETYLTRANSFERASES

In 1995, yeast HAT1 (histone acetyltransferase 1) (Table 2) was identified as the first HAT (58). Although HAT1 was considered to be mainly localized in the cytoplasm to acetylate nascent histones for deposition, recent studies indicate that this acetyltransferase also exists in the nucleus to regulate gene silencing (59). The importance of HATs in gene regulation began to be widely considered in 1996 when HAT activity was shown to be intrinsic to several known transcriptional co-activators such as Gcn5 (general control non-derepressible 5) (13), PCAF (60), p300 (E1A-associated 300 kDa protein) (43), CBP (CREB-binding protein) (43,44) and TAF$_{II}$250 (TBP-associated factor of 250 kDa) (61). Subsequently, additional proteins were shown to possess HAT activity (Table 2). As listed in Table 2, these proteins include
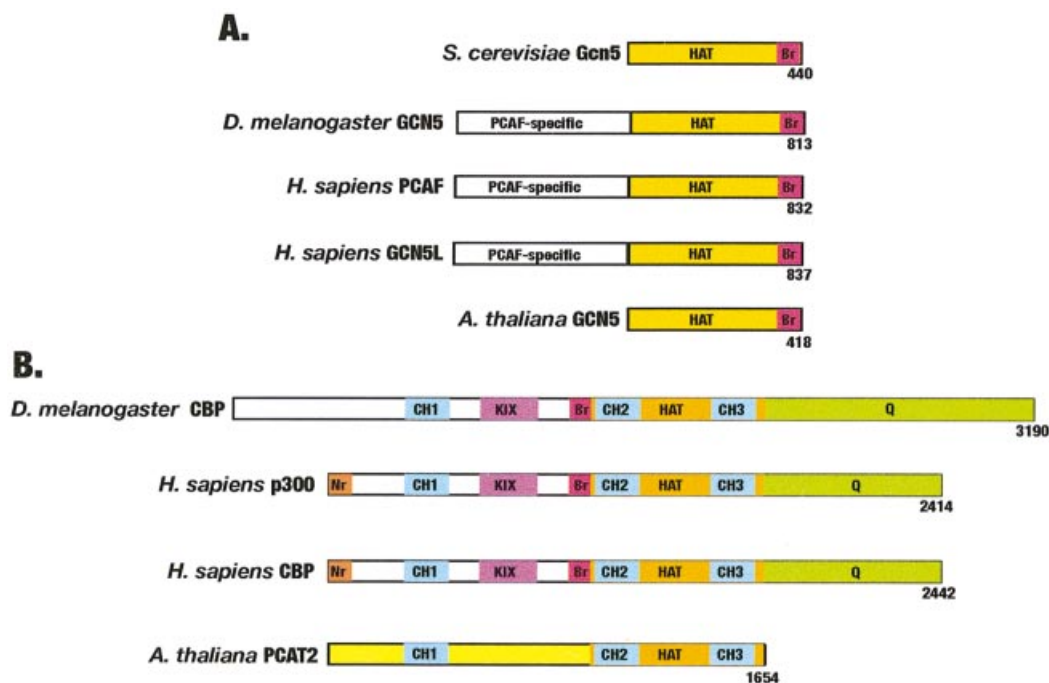
Figure 1. Schematic illustration of the Gcn5/PCAF (**A**) and p300/CBP (**B**) families of HATs. Br, bromodomain; Nr, nuclear receptor-interacting box; CH, cysteine/histidine-rich module; KIX, phospho-CREB interacting module; Q, glutamine-rich domain. Numbers on the right correspond to total residues that each protein possesses. In *A.thaliana* there are five p300/CBP acetyltransferase-related proteins (PCAT1–5), one of which (PCAT2) is depicted here.

the nuclear receptor co-activators SRC-1 (steroid receptor coactivator 1) and ACTR (activator of retinoid receptor, also known as AIB1 for amplified in breast cancer 1) (62,63), the transcriptional co-activator CIITA (major histocompatibility class II activator) (64), the DNA-binding transcription factor ATF2 (65), the transcriptional mediator Nut1 (66), the transcription initiation factor TFIIIC (67), the transcription elongation factor Elp3 (68), the yeast protein Hpa2 (69), CDY (chromodomain Y) and its homolog CDYL (CDY-like) (70) and the MYST family of proteins (20,22,71). p300, CBP and PCAF also acetylate transcription factors and other proteins (20,23). Some HATs display autoacetylating activity (42–45). TFIIB acetylates itself, but does not possess any detectable HAT activity (26,69). MCM3AP (MCM3 acetylating protein), Eco1 (establishment of cohesion 1) and ARD1 (a known N^{α}-acetyltransferase) are three other LATs that were not identified first as HATs (24,25,27). Quite interestingly, acetyl-CoA synthetase is responsible for the acetylation of CheY in *E.coli* (56,57).

According to sequence similarity, known LATs can be organized into different groups (Table 2). As one major group of nuclear HATs, the Gcn5/PCAF family is composed of Gcn5, PCAF and related proteins. As illustrated in Figure 1A, yeast Gcn5 possesses a HAT domain and a bromodomain and is highly homologous to the C-terminal halves of human PCAF and GCN5L (mammalian GCN5 long form) (60,72–75). Like *Drosophila* GCN5, mammalian PCAF and GCN5L possess PCAF-specific N-terminal domains (Fig. 1A) (74). A recent study indicates that GCN5 from the worm *Schistosoma mansoni* has a similar domain organization (76). Numerous studies indicate that these HATs function as histone-

acetylating transcriptional co-activators (4,6,21). Besides histones, PCAF also acetylates non-histone proteins (20,23).

The p300/CBP family is another major group of nuclear HATs that has been extensively characterized (Fig. 1B) (77–79). Like PCAF, both p300 and CBP are transcriptional co-activators able to acetylate histones and non-histone proteins. Reminiscent of PCAF and GCN5L, p300 and CBP form a pair of homologous HATs in mammals (Fig. 1). *Drosophila* CBP is larger, but possesses a similar domain organization (Fig. 1B). As in *Drosophila*, there is also only one p300/CBP ortholog in *Caenorhabditis elegans* (78). In *Arabidopsis thaliana* there are five proteins displaying sequence similarity to the HAT domains of p300 and CBP (Fig. 1B) (80,81); functions of these novel proteins remain to be determined.

The MYST family of proteins constitutes a third major group of nuclear HATs (Table 2 and Fig. 2). Compared with the Gcn5/PCAF and p300/CBP groups, the MYST family is larger, more diverse and not so well characterized. Despite their similar HAT domains, MYST proteins play different roles in various cellular processes. In light of their unique structure and function, these acetyltransferases will be discussed in detail in the next section.

In addition to these three major groups of HATs, more than a dozen other proteins have been shown to possess acetyltransferase activity (Table 2). Like members of the Gcn5/PCAF family, HAT1, Nut1, Elp3, Hpa2/Hpa3, MCM3AP, Eco1 and ARD1 share three or four similar motifs with various *N*-acetyltransferases and thus belong to the Gcn5-related *N*-acetyltransferase (GNAT) superfamily (4,6,24,25, 27,82). One of the shared motifs is the classical acetyl-CoA-binding site, which is also present in the MYST family
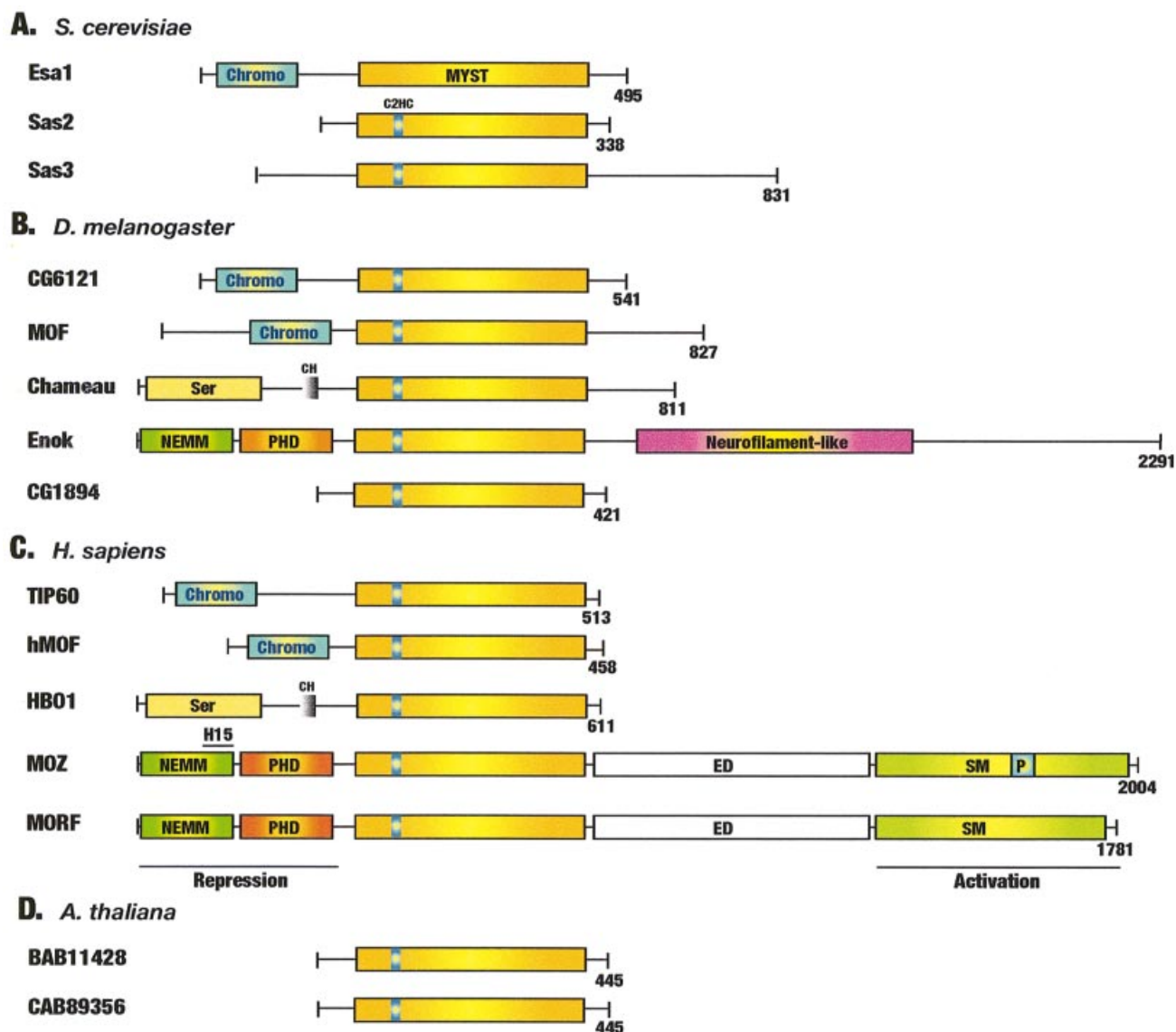
Figure 2. Domain organization of MYST proteins from *S.cerevisiae* (**A**), *Drosophila* (**B**), human (**C**) and *A.thaliana* (**D**). Chromo, chromodomain; Ser, serine-rich domain; CH, cysteine/histidine-rich motif; H15, linker histones H1- and H5-like domain; NEMM, N-terminal part of Enok, MOZ or MORF; PHD, PHD zinc finger; ED, glutamate/aspartate-rich region; SM, serine/methionine-rich domain. The SM domain of MOZ has an insertion of a proline/glutamine-stretch (labeled P). Bars below the N-terminal and SM domains of MORF denote its transcriptional repression and activation domains, respectively. Numbers on the right correspond to the total residues that each protein has.

members and ATF2 (6,65,83,84). In contrast, such a motif is absent in other known LATs, so there may be different acetyl-CoA binding modes. Indeed, CDY and CDYL do not have the classical acetyl CoA-binding motif, but display some sequence similarity to several CoA-utilizing enzymes (70).

Most HATs exist as stoichiometric multisubunit complexes *in vivo* (Table 2). The complexes are typically more active than their respective catalytic subunits and display distinct substrate specificities (85–88), suggesting that associated subunits regulate the activities of the respective catalytic subunits. In addition, non-catalytic subunits are also involved in recruiting substrates for targeted action to ensure the specificity. Amazingly, one HAT can be the catalytic subunit of multiple complexes. As listed in Table 2, GCN5L forms at least two distinct multisubunit complexes (89–91), and yeast

Gcn5 is the catalytic subunit of four complexes (85,92–96; reviewed in 6). Notably, recent studies indicate that Ubp8, a deubiquitinating enzyme present in two Gcn5 complexes, controls the deubiquitination of histone H2B and methylation of histone H3 (97–99). Therefore, the diversity of multisubunit complexes adds another level of complexity to the already diverse superfamily of LATs.

Some known LATs display weak activity towards substrates tested, so an interesting question is whether low levels of activity observed *in vitro* have any biological significance. One possibility is that the weak activity is not intrinsic, but rather due to an associated HAT. For example, the HAT activity observed with BRCA2 appears to be from associated PCAF (100). It is noteworthy that a weak or null activity observed with a potential LAT *in vitro* could also be a 'false

negative'. A given substrate used may not be the real one since many proteins are acetylated. Moreover, HATs form multi-subunit complexes with different activities and substrate specificities (85–87), so activity data obtained with recombinant catalytic subunits could be potentially misleading. Activities of LATs are dynamically regulated by different mechanisms (see below), so the situation could be even more complicated *in vivo*. For example, neither Sas2 nor its complex acetylates nucleosomal histone H4 *in vitro* (101), but Sas2 appears to do so *in vivo* (102,103). Therefore, different experimental approaches are needed to address whether a potential LAT with weak activity *in vitro* is an authentic one *in vivo*.

SIMILAR ACETYLTRANSFERASE DOMAINS BUT DIVERSE FUNCTIONS: THE MYST FAMILY OF PROTEINS

Different MYST proteins

The acronym MYST is from its four founding members: human MOZ (monocytic leukemia zinc finger protein) (83), yeast Ybf2 (renamed Sas3, for something about silencing 3) (84,104), yeast Sas2 (84) and mammalian TIP60 (HIV Tat-interacting 60 kDa protein) (105–107). As illustrated in Figure 2A, a third MYST protein in *Saccharomyces cerevisiae* is Esa1 (essential Sas2-related acetyltransferase 1) (108,109). In *Drosophila* (Fig. 2B), there are five members, including Mof (male-absent on the first) (110,111), Enok (Enoki mushroom) (112), Chameau (camel in French) (113) and two uncharacterized MYST proteins (CG6121 and CG1894). In humans (Fig. 2C), besides MOZ and TIP60, there are hMOF (ortholog of *Drosophila* Mof), HBO1 (HAT bound to ORC1, a Chameau ortholog) (114) and MORF (MOZ-related factor) (45). Among these, TIP60 is most similar to *Drosophila* CG6121 and yeast Esa1 (Fig. 2A–C). There are two uncharacterized MYST proteins in *A.thaliana* (Fig. 2D) (81). Similar proteins also exist in *Schizosaccharomyces pombe* and parasitic protozoa (22). Therefore, this family appears to have members in all eukaryotes.

Domain organization of MYST proteins

Members of this family possess highly homologous ~370 residue MYST domains (identity, 36–77%; similarity, 54–84%) (Fig. 2). Structural analysis has revealed that the MYST domain of Esa1 uses an acetyl-cysteine intermediate in the acetylation reaction, so the catalytic mechanism involved is different from that shared by members of the GNAT superfamily of acetyltransferases (115). C_2HC fingers are present in all MYST domains except for that of Esa1 (Fig. 2). Despite the absence of zinc and three of the four chelating residues, the corresponding region of Esa1 forms a classical TFIIIA-type zinc finger fold (116). The C_2HC fingers of Sas3, Mof and MOZ are known to be essential for HAT activity (104,117,118). A mutation in the C_2HC finger of *Drosophila* Enok affects brain development (112). The C_2HC finger of Mof binds to nucleosomes *in vitro* (117), whereas the C_2HC finger of TIP60 is essential for interaction with the translocation E26 transforming-specific (ETS) leukemia protein TEL (119). Therefore, C_2HC zinc fingers are important *in vitro* and *in vivo*.

Besides MYST domains, this family of proteins contains other structural modules (Fig. 2). One such module is the chromodomain (120), conserved among Esa1, Mof and TIP60 (Fig. 2A–C). The chromodomain of Mof binds to roX (RNA on the X) RNAs and targets the complex to the male fly X chromosome for gene dosage compensation (121). In comparison, the chromodomain of HP1 (heterochromatin protein 1) recognizes Lys9-methylated histone H3 (122,123). Therefore, it will be interesting to determine what roles the chromodomains of Esa1 and TIP60 may have. The PHD (plant homeodomain-linked) zinc finger is another recognizable module (Fig. 2). Two PHD fingers are found in the N-terminal parts of Enok, MOZ and MORF (45,83,112,124). The PHD domains of MOZ and MORF are much more similar to each other than to those of Enok and display high sequence homology to Neuro-D4 and Requiem, two potential transcription factors that do not have MYST domains (83). PHD fingers are also known as LAP (leukemia-associated protein) domains and have been found in many chromatin regulators (125,126). Mutations in PHD fingers of several chromatin regulators contribute to a variety of human diseases (127,128). Atypical PHD zinc fingers with similarity to RING fingers have been shown to function as E3 ubiquitin ligases (129), but it is unclear whether this is a common functional feature of all PHD fingers (130). Interestingly, PHD fingers from several chromatin regulators bind to phosphoinositides and are thus implicated in nuclear lipid signaling (131). The PHD zinc fingers of MOZ display phosphoinositide-binding activity, raising the interesting possibility that phosphoinositides act through PHD zinc fingers and regulate the functions of Enok, MOZ and MORF.

Besides PHD fingers, MOZ and MORF share their extreme N-terminal regions with Enok (Fig. 2B and C), referred to as NEMM (N-terminal region in Enok, MOZ or MORF) domains. The NEMM domains of MOZ and MORF, but not that of Enok, display some sequence similarity to the globular domains of linker histones H1 and H5. The functional significance of this similarity remains to be determined. These H1- and H5-like regions, known as H15 domains, may mediate self-association and interaction with core histones and nucleosomes since the globular domains of histones H1 and H5 are known to have similar activities (132,133). In addition, Enok possesses an uncharacterized neurofilament protein-like domain that is missing in other MYST proteins (Fig. 2B) (112). At the C-terminal ends of MOZ and MORF (Fig. 2C) are serine- and methionine-rich regions, which are known as SM domains and possess potent transcriptional activation potential (45,134). Therefore, MYST proteins have diverse domain organizations.

Different multisubunit complexes of MYST proteins

Consistent with their diverse domain organizations, MYST proteins exist as distinct multiprotein complexes *in vivo*. Yeast Esa1, Sas2 and Sas3 are the catalytic subunits of different multiprotein complexes (Table 2). The Esa1 complex NuA4 contains 12 subunits, including Tra1 (TRRAP homolog 1), actin, Arp4 (actin-related protein 4), Epl1 (Enhancer of Polycomb-like protein 1), Yng2 (homolog of mammalian ING1, for inhibitor of growth 1) and Yaf9 (homolog of the leukemogenic human protein AF9) (94,135,136). Among these subunits, Esa1, Epl1 and Yng2 form a highly active but

much smaller core complex, termed Piccolo NuA4 (88). Sas2 and Sas3 are the catalytic subunits of two trimeric complexes: Sas2 associates with Sas4 and Sas5 (AF9 homolog), whereas Sas3 interacts with Taf30 (AF9 homolog) and Yng1 (ING1 homolog) (137–139). Since Esa1 and Sas3 associate with homologs of mammalian ING1, phosphoinositides may bind to the complexes and regulate their functions. In *Drosophila*, one MYST complex has been characterized (140). Mof in male flies is part of a dosage compensation complex that contains Msl1 (male-specific lethal 1), Msl2, Msl3, Mle (maleless, homolog of mammalian RNA helicase A) and two non-coding RNA molecules, roX1 and roX2. Notably, this is the only HAT complex known to contain RNA. The chromodomains of Mof and Msl3 are able to mediate RNA binding (121). In mammals, the TIP60 complex has been purified and characterized (141,142). It shares similar subunits with the Esa1 complex, including TRRAP (transformation/transcription domain-associated protein), actin, BAF53 (actin-related protein) and EPC (Enhancer of Polycomb-like protein). However, the TIP60 complex also possesses unique subunits such as p400 (SWI2/SNF2-related ATPase), two RuvB-like proteins and DMAP1 (DNMT1-associated protein 1) (141,142). Originally identified as an essential cofactor for the oncogenic transcription factors c-Myc and E2F (143), TRRAP is an ATM/PI-3 kinase-like protein shared by the PCAF (144), GCN5L (89–91), TIP60 (141) and p400 complexes (145) (Table 2). As the yeast homolog of TRRAP, Tra1 is a common subunit of the Gcn5 and Esa1 complexes (92–96). In contrast, the Sas2, Sas3 and Mof complexes do not possess proteins similar to TRRAP. It is expected that human MOF does not associate with TRRAP, but it remains unclear whether other MYST proteins, such as HBO1, MOZ and MORF, interact with TRRAP.

### Diverse functions of MYST proteins

As suggested by their unique domain organizations and different complex compositions, MYST proteins are involved in regulating various biological processes. In agreement with the fact that the NuA4 subunit Yng2 is homologous to the candidate tumor suppressor ING1 (146,147), Esa1 is important for DNA repair and cell cycle progression (108,109,148). The Esa1 complex has also been linked to epigenetic control, gene regulation and cellular response to spindle stress (135,136). In support of its role in yeast gene silencing (84), Sas2 opposes the action of the deacetylase Sir2 to establish the boundary between euchromatin and heterochromatin (102,103). Sas3 was originally identified as a regulator of gene silencing (84), whereas its complex was recently shown to be involved in regulating transcriptional elongation (137). *Drosophila* Chameau is important for heterochromatin-mediated gene silencing and Mof is a major player in gene dosage compensation in male flies (110,112). As for mammalian MYST proteins, TIP60 plays an important role in apoptosis and DNA repair (141).

Different lines of evidence suggest that MYST proteins are also targeted to specific promoters to regulate transcription. Through interacting with DNA-binding transcription factors, yeast Esa1 is recruited to regulate the expression of ribosomal proteins (149). The tumor suppressor p53 interacts with ING proteins and its ability to activate transcription in yeast is modulated by Yng1 and Yng2, two ING homologs that are

subunits of the Sas3 and Esa1 complexes, respectively (147,150). TIP60 not only functions as a transcriptional co-repressor for TEL (119) and STAT3 (151), but also as a coactivator for androgen receptor (152,153), NF-κB (154) and c-Myc (155). Through a unique NPxY motif within its MYST domain, TIP60 interacts with the WW domain of Fe65 and potentiates transcription mediated by the APP (amyloid-β precursor protein) cytoplasmic domain (154,156–158). Therefore, TIP60 regulates transcription in a context-dependent manner. Originally identified as a protein interacting with ORC1, an ORC (replication origin recognition complex) subunit (114), HBO1 has recently been found to function as a transcriptional co-repressor for androgen receptor (159). Human MOF is part of a complex implicated in activating the B-myb promoter (160). MOZ and MORF possess transcriptional repression and activation domains (45,134,161), suggesting that these two HATs are potential transcriptional co-regulators. Indeed, MORF is present in a transcriptional co-activator complex associated with the nuclear receptor PPARα (162). Both MOZ and MORF physically and functionally interact with Runx1 and Runx2 (161,163,164), two Runt domain transcription factors important for cell growth and differentiation in different tissues (165–168). In agreement with this, down-regulated expression of mouse MORF, known as Querkopf (squarehead in German), leads to defects in osteogenesis and neurogenesis (169). Therefore, compared with members of the Gcn5/PCAF and p300/CBP families, MYST proteins are much more diverse in domain organization, multiprotein complex formation and biological function.

REGULATION OF LYSINE ACETYLTRANSFERASES

With more information available on the structure and function of different LATs, the regulation of their enzymatic activities has become an important issue in the past few years. Emerging data suggest that multiple mechanisms are involved. First, as an essential cofactor for different acetyltransferases, acetyl-CoA also stabilizes GCN5 and PCAF (42). Second, as described above, formation of stoichiometric multisubunit complexes modulates the specific activities and substrate specificities of different LATs. Third, the enzymatic activities of PCAF, p300 and CBP are regulated by interaction with transcription factors such as p/CIP (170), Twist (171), vIRF (172), Zta (173), HOX proteins (174), PU.1 (175) and the early B-cell factor (176); the ubiquitin ligase MDM2 (177–179); the protein kinase RSK2 (180); and viral proteins like E1A (170,171,181,182), E1B (183), T antigen (184), E7 (185) and Tat (186). Fourth, LATs are subject to covalent modifications such as phosphorylation (65,187), acetylation (37,46), ubiquitination (188–190) and sumoylation (191). Fifth, LATs are degradated by caspases, calpains and ubiquitin-dependent proteasomes (188–190,192). Sixth, subcellular compartmentalization is an important regulatory mechanism for HATs. For example, HAT1 binds to 14-3-3 proteins (193) and TIP60 is sequestered to the cytoplasm in a signal-dependent manner (154,156,158,194). Finally, while p300, CBP, MOZ and MORF possess PHD fingers (Figs 1 and 2), yeast Esa1 and Sas3 associate with PHD finger-containing subunits (6,22). PHD fingers are implicated in phosphoinositide binding and may thus provide structural modules for integrating nuclear
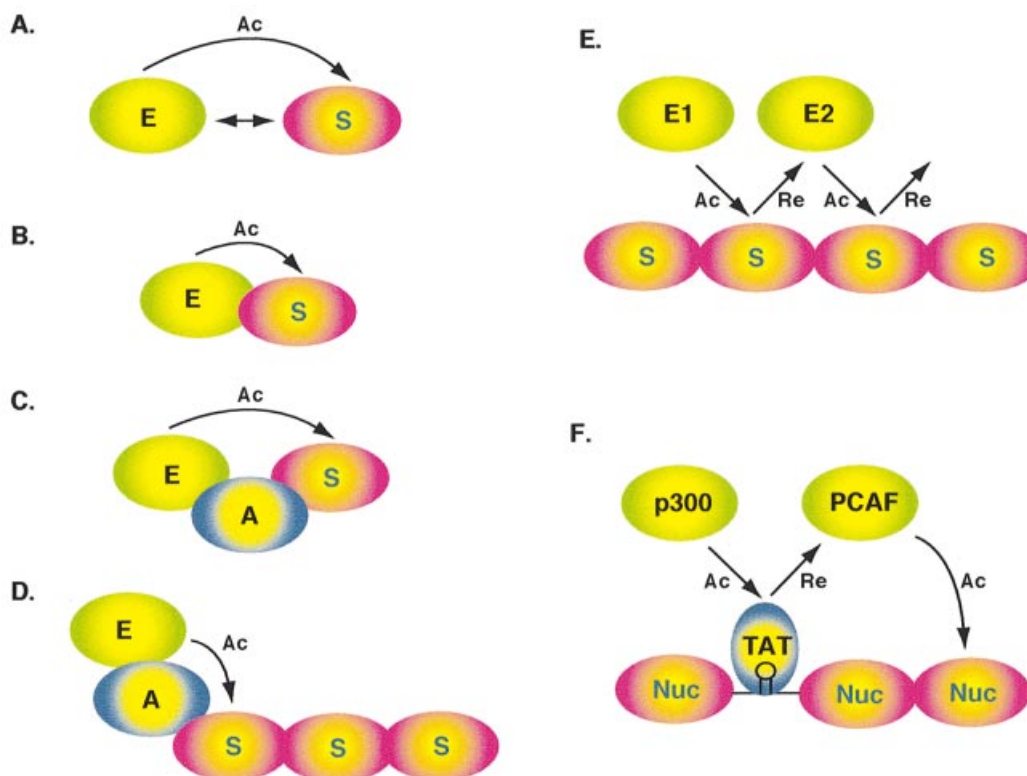
Figure 3. Diagrams showing how LATs may recognize their substrates. (**A**) In the 'hit-and-run' model, the enzyme–substrate interaction is transient and the substrate dissociates from the enzyme once the reaction is complete. The substrate specificity of the enzyme is mainly determined by its association with the modification site on the substrate. The modification site may reside within a consensus sequence. E, enzyme; S, substrate; Ac, acetylation. (**B** and **C**) In the 'attract-and-hit' models, the enzyme brings the substrate to the physical proximity either through association with a docking site on the substrate (B) or through the help of an adaptor protein (C). After the reaction, the enzyme may remain associated with the substrate. (**D**) In the 'targeted action' model, the enzyme is recruited to a polymer substrate through an adaptor protein. The adaptor recognizes a specific monomer of the polymer and thus determines the substrate specificity. (**E**) The 'relay' model applies to LATs that possess acetyllysine-binding domains. One acetyltransferase molecule (E1) acetylates one monomer of a polymer substrate and the acetylated monomer then recruits (Re) a second acetyltransferase molecule (E2) via its acetyllysine-binding domain. Acetylation by E2 in turn recruits E1 and leads to the expansion of an acetylation zone. If E1 is the same as E2, the acetylation process is self-perpetuating. (**F**) Production of HIV TAR RNA at the promoter leads to the recruitment of Tat. Upon acetylation at Lys50 by p300, Tat interacts with the bromodomain of PCAF, which is then targeted to acetylate nearby nucleosomes.

lipid signals (131), so activities of these acetyltransferases may be regulated by nuclear signaling events.

HOW DO LYSINE ACETYLTRANSFERASES RECOGNIZE THEIR SUBSTRATES?

In addition to the regulatory mechanisms just described, substrate recognition is another point for controlling acetylation. A relevant question is how the specificity is achieved. The classical 'hit-and-run' model can be used to depict how HATs recognize free histone substrates (Fig. 3A). For example, HAT1 acetylates newly synthesized histones in such a mode (195,196). HATs also adopt 'attract-and-hit' mechanisms. To bring substrates into their physical proximity, HATs and other LATs may either bind directly to their substrates (Fig. 3B) or interact with their substrates through adaptor proteins (Fig. 3C). Since physical proximity increases the local substrate concentration, 'attract-and-hit' modes are more efficient than 'hit-and-run' ones. For example, when the WD40-repeat histone-binding protein HAT2 is present, HAT1 is 10 times more active (197). With polymer substrates such as chromatin, region-specific acetylation is sometimes necessary

(Fig. 3D). To specifically modify chromatin, HATs are often recruited to carry out targeted acetylation, which is reminiscent of the indirect 'attract-and-hit' mechanism (Fig. 3C). In this scenario, subunits associated with a HAT may modulate the targeting specificity. As stated above, incorporation of one HAT into different complexes adds another level of diversity for substrate targeting. Like chromatin, microtubules are polymers, so a tubulin acetyltransferase may also need to be targeted. While the DNA sequence marks the position of a given nucleosome within a chromatin array and thus dictates region-specific recruitment of HATs for acetylation, microtubules do not have such a marking system. Region-specific tubulin acetylation on a microtubule may be achieved during polymerization. As illustrated in Figure 1, most members of the Gcn5/PCAF and p300/CBP families contain bromodomains, so these acetyltransferases are able to participate in 'relay' reactions (Fig. 3E), with one enzyme executing the initial acetylation in a polymer substrate to create a binding site for the bromodomain of another enzyme, which then initiates another round of acetylation to trigger a cascade of reactions. This may be one means to execute chromatin domain-, chromosome- and genome-wide acetylation (198). A

slightly different scenario is that with acetylating activities coupled to acetyllysine-binding bromodomains, two LATs cooperate with each other to carry out sequential acetylation of different substrates. Such a mode of action has been elegantly demonstrated for p300 and PCAF in their sequential acetylation of Tat and histones (Fig. 3F) (199,200). Therefore, LATs utilize different means to cope with various types of substrates.

HOW DOES LYSINE ACETYLATION EXERT ITS EFFECTS?

Once a lysine residue is acetylated, a mechanistic question is how such a modification may affect protein function. It appears that both 'loss-of-function' and 'gain-of-function' mechanisms are involved. Regarding the former, acetylation of the ε-amino group of a lysine residue neutralizes the positive charge, so the modification may affect interaction of the lysine residue with DNA, RNA and proteins. Such a mechanism may operate with chromatin since the DNA backbone is negatively charged. Indeed, histone acetylation has been shown to affect the nucleosomal structure and the stability of nucleosomal arrays (201–204). Alternatively, acetylation may render the ε-amino group unable to form hydrogen bonds. For example, Lys11 of Alba is involved in forming a hydrogen bond important for oligomerization, so acetylation of this residue inhibits oligomerization (8,9). Acetyl-CoA synthetase from *S.enterica* provides another unique example of a 'loss-of-function' effect (10). Lys609 of this enzyme is part of the catalytic center, so acetylation of this residue inhibits the enzymatic activity.

In eukaryotic cells, the ε-amino group of a lysine residue is also subject to methylation and modification by ubiquitin and ubiquitin-like proteins such as NEDD8 and SUMO (Fig. 4). Different modifications are mutually exclusive, thus leading to their potential competition. It has recently been shown for SREBP and Smad7 that acetylation directly competes with ubiquitination for the same lysine residues to increase protein stability (51,205). Acetylation and methylation of histone H3 at Lys9 have completely opposite functional consequences, with the former associated with active chromatin and the latter linked to heterochromatin or inactive chromatin (2,5). Since acetylation blocks methylation, histone deacetylases are needed to remove the acetyl group from Lys9 and clear the way for subsequent methylation and thus the establishment of inactive chromatin (206,207).

As for 'gain-of-function' mechanisms, the addition of an acetyl group to a lysine residue creates a new surface for protein association. Reminiscent of domains that recognize phosphoproteins (208,209), bromodomains function as structural modules specific for acetyllysine-containing motifs (Fig. 4). It has been demonstrated that several chromatin regulators use bromodomains to recognize acetyllysine (210–216). Bromodomains are found in many proteins and sequence variations may dictate their binding specificity (217). Some proteins contain multiple bromodomains, which may co-operate with each other to increase the affinity for binding partners with multiple acetylated lysine residues (211). Acetylation is also known to stimulate the association with proteins that do not contain bromodomains (27,218). Different types of structural modules have been identified for
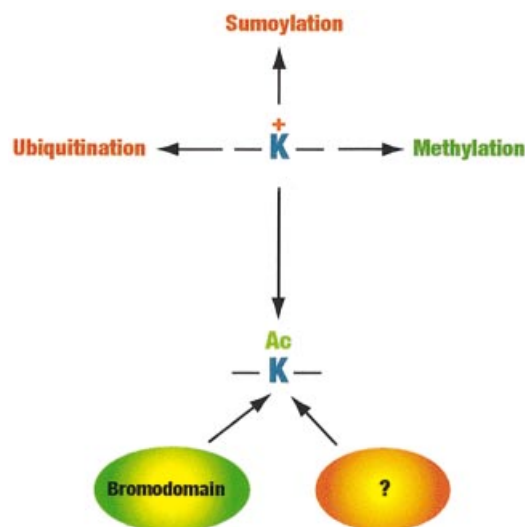

Figure 4. The ε-amino group of a lysine (K) residue is subject to multiple covalent modifications, including ubiquitination, sumoylation, methylation and acetylation (Ac). Acetylation neutralizes the positive charge of the lysine side chain, affects its ability to form hydrogen bonds and creates a new binding surface for protein modules such as the bromodomain.

phosphotyrosine (209,219), so an interesting question to be addressed is whether there are additional acetyllysine-recognizing modules (Fig. 4).

ROLES OF LYSINE ACETYLTRANSFERASES IN LEUKEMIA AND OTHER MALIGNANCIES

Consistent with the essential roles of LATs in different biological processes, molecular and genetic studies have revealed that these enzymes are also important players in human pathology. Among others, the following lines of evidence strongly suggest that several HATs are directly linked to oncogenesis: (i) the viral oncoproteins such as E1A and large T antigen target p300 and CBP (77,78,220); (ii) E1A also interacts with PCAF and TRRAP, a subunit of multiple HAT complexes (6,143,220,221); (iii) the proto-oncoprotein SYT targets p300 (222); (iv) p300, CBP and PCAF associate with and modify various transcription factors, such as p53, Rb, E2F, H1Fα and E2A, that play key roles in controlling different cellular programs (21,77–79); (v) oncogenic transcription factors c-Myc and E2F bind to TRRAP (143); (vi) the tumor suppressor p53 also binds to ING proteins, homologs of which have been found in HAT complexes (147); (vii) MOZ and MORF interact with Runx1 (161,163,164), the most frequent target of leukemia-associated chromosomal translocations (166,168); (viii) TIP60 associates with the androgen receptor and has been implicated in the development of prostate cancer (152,153,223); (ix) TIP60 is involved in regulating apoptosis and its yeast homolog Esa1 is essential for cell cycle progression (108,109,141).

Among known HATs (Table 2), p300 and CBP have been considered as tumor suppressors (77–79). Consistent with this notion, monoallelic mutation of the *CBP* locus is the genetic basis for Rubinstein–Taybi syndrome and patients with this syndrome exhibit an increased risk of developing malignant tumors (224). Biallelic mutations of the *p300* locus have been
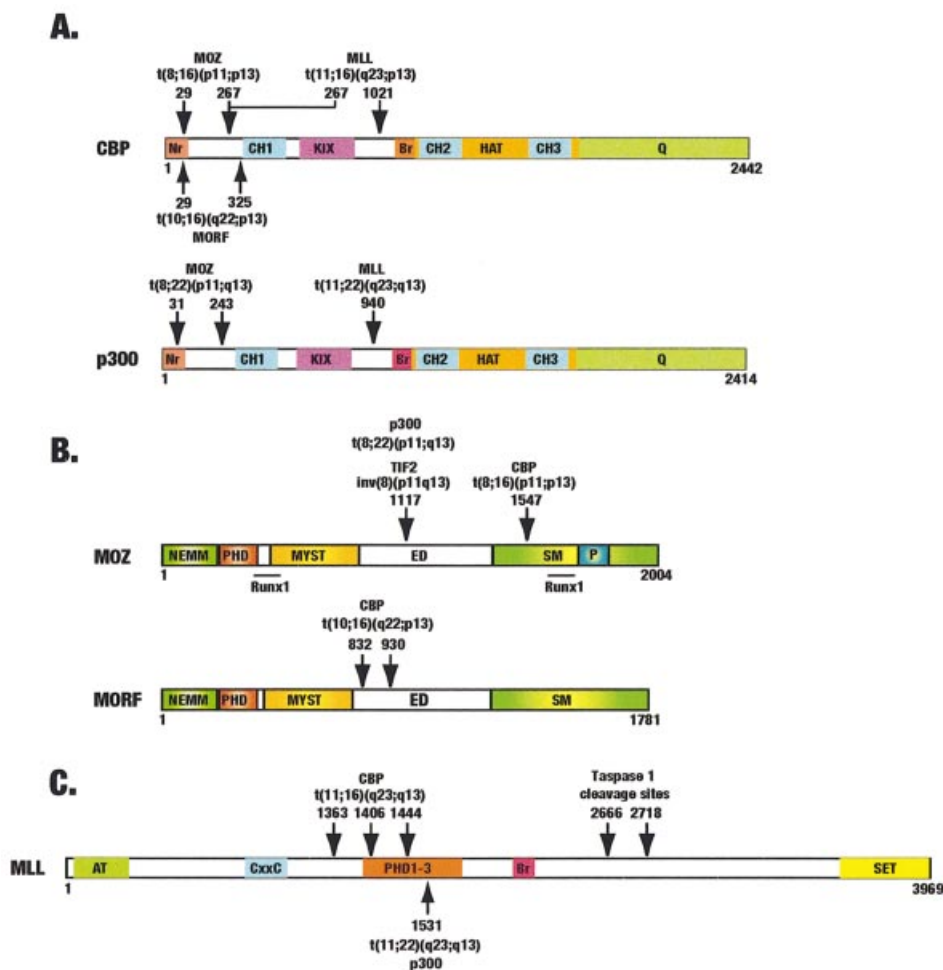
Figure 5. Schematic illustration of chromosomal abnormalities associated with p300/CBP (**A**), MOZ/MORF (**B**) and MLL (**C**). The breakpoints are indicated with arrows and numbers at their ends represent the amino acid positions. For MLL, the Tapase 1 cleavage sites are also indicated. AT, AT-hook DNA-binding domain; CxxC, zinc finger; SET, histone methyltransferase domain. Other structural domains are labeled as in Figures 1 and 2.

identified in human cancers of epithelial origin (225,226) and exogenous expression of p300 is able to suppress the growth of human carcinoma cells *in vitro* (227). Moreover, p300 and CBP play distinct but essential roles in hematopoiesis, and mice with inactivated alleles of the *p300* and *CBP* loci develop hematological malignancies (228–231).

Studies of chromosomal abnormalities in leukemia patients have provided additional support for the direct involvement of HATs in human cancer. The *p300* and *CBP* genes are located on chromosomes 16p13 and 22q13, respectively, and have been shown to be rearranged in chromosomal translocations associated with leukemia or treatment-related myelodysplastic syndrome (Fig. 5A). Known fusion partners are MOZ, MORF and MLL (mixed lineage leukemia) (Fig. 5). The MLL gene, located at 11q23, is fused to the *p300* and *CBP* genes in the translocations t(11;22)q23;q13) and t(11;16)(q23;p13), respectively (Fig. 5A and C) (232–238). These translocations lead to the production of different MLL-p300 and MLL-CBP fusion proteins, in which the bromodomain, HAT domain and Q region of p300 or CBP are linked to the N-terminal part of MLL. The *MOZ* gene, located at 8p11, is fused to that of CBP in two t(8;16)(p11;p13) translocations (Fig. 5B), which gives

rise to MOZ-CBP proteins containing the N- and C-terminal parts of MOZ and CBP, respectively (83,239). In two t(8;22)(p11;q13) translocations, the *MOZ* gene is fused to the *p300* gene, generating MOZ-p300 fusion proteins (240,241). In the t(8;16) and t(8;22) translocations, the reverse transcripts expressing CBP-MOZ or p300-MOZ are not always produced, suggesting that the MOZ-CBP and MOZ-p300 fusion proteins are responsible for the leukemogenesis. These fusion proteins possess the NEMM, PHD and MYST domains of MOZ, as well as the CH1, KIX, bromodomain, HAT domain and Q region of CBP or p300 (Fig. 5A and B). Notably, the SM domain of MOZ is missing from these fusion proteins.

Besides p300 and CBP, other partners are also involved in the fusion with the *MOZ* gene. In two slightly different inv(8)(p11q13) chromosomal inversions (Fig. 5C), the *MOZ* gene is fused to the *TIF2* gene located at 8q13, creating a protein with the N-terminal part of MOZ fused to the C-terminal part of TIF2 (242–244). TIF2 is a member of the p160 family of nuclear receptor co-activators known to interact with p300 and CBP. A recent study indicates that the *MOZ* gene is also rearranged in a t(2;8)(p23;p11)

translocation associated with therapy-related myelodysplastic syndrome, but the translocation partner remains to be identified (245).

The sequence similarity between MOZ and MORF suggests that the *MORF* gene is rearranged in a manner similar to the *MOZ* gene (45). Indeed, the *MORF* gene was recently found to be rearranged and fused to the *CBP* gene in a recurrent t(10;16)(q22;p13) translocation associated with acute myeloid leukemia (Fig. 5A and C) (246,247). A slightly different t(10;16)(q22;p13) translocation, associated with therapy-related myelodysplastic syndrome, also leads to fusion of the *MORF* gene to the *CBP* gene (247). The resulting MORF-CBP fusion proteins are structurally similar to the MOZ-CBP and MOZ-p300 fusion proteins described above.

All of the above chromosomal abnormalities suggest that aberrant acetylation by mistargeted HATs plays a causative role in leukemogenesis. Indeed, one MLL-CBP fusion protein has been analyzed in mice and found to generate a myelodysplastic syndrome that evolves into myeloid leukemia (248). The bromodomain and HAT domain of CBP are the only modules needed for the leukemogenic activity, suggesting that the N-terminal part of MLL directs the two CBP domains for aberrant acetylation and subsequently leads to leukemogenesis. MLL is processed by Taspase 1 cleavage and the resulting N- and C-terminal fragments remain associated within the same histone methyltransferase complex (Fig. 5C) (249). It is unclear whether the MLL-CBP fusion proteins are still able to bind the processed C-terminal fragment of MLL. Potential targets of MLL-CBP are members of the HOX gene family (250,251), so MLL-CBP may lead to abnormal expression of these genes and cause the subsequent development of leukemia (Fig. 6A).

A MOZ-CBP fusion protein from t(11;16)(q23;p13) has been characterized (161). This fusion protein inhibits Runx1-dependent transcription and blocks the differentiation of murine myeloid M1 cells to macrophages. Moreover, the HAT domain of CBP appears to be important for the repressive activities. Two slightly different MOZ-TIF2 fusion proteins from inv(8)(p11q13) chromosomal inversions have recently been shown to display oncogenic potential in both *in vitro* transformation and *in vivo* transplant assays (118). The C_2HC zinc finger of MOZ (Fig. 2) is essential, whereas its acetyl-CoA-binding motif only modulates the penetrance and phenotype of the resulting diseases. For TIF2, only its CBP-interacting domain is essential, so the recruitment of CBP to MOZ is responsible for leukemogenesis. This finding suggests that the underlying molecular mechanism is very similar to that used by MOZ-CBP. Therefore, both MOZ-CBP and MOZ-TIF2 may repress Runx1-dependent gene expression and cause the development of leukemia (Fig. 6B). Although both MLL-CBP and MOZ-CBP are leukemogenic, their mechanisms of action are quite different, with the former being an activator and the latter functioning as a repressor (Fig. 6).

CONCLUDING REMARKS

As a common post-translational modification, lysine acetylation is known to occur not only at the N-terminal tails of core histones but also within other eukaryotic proteins, including about 40 transcription factors, a chromatin remodeler, one
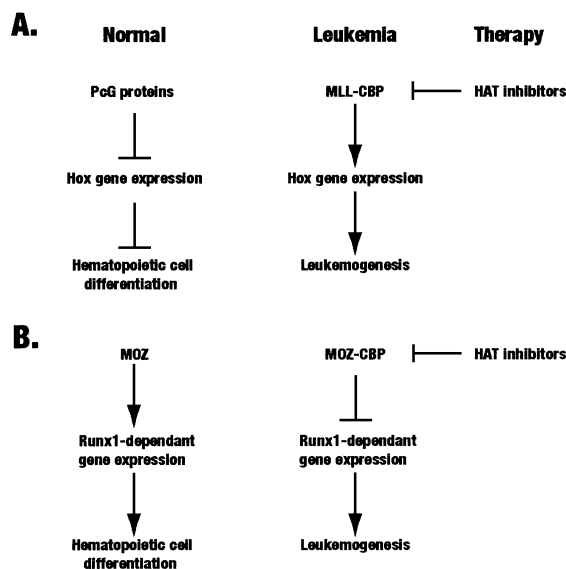
Figure 6. Models explaining how aberrant HATs may lead to leukemogenesis. (**A**) In normal hematopoietic cells (left), Polycomb group (PcG) proteins repress the expression of HOX genes such as Hox7a and Hox9a, whereas the histone methyltransferase MLL relieves the repression to maintain suitable expression levels when and where it is necessary. The t(11;16)(q23;p13) translocations (Fig. 5) produce MLL-CBP fusion proteins. Unlike wild-type MLL, these fusion proteins cause aberrant acetylation at the HOX loci, which in turn up-regulates the expression of HOX genes and causes the subsequent development of leukemia (middle). A similar mechanism may apply to MLL-p300 fusion proteins derived from the t(11;22)(q23;q13) translocations (Fig. 5). Therefore, inhibitors of p300 and CBP may be of therapeutic value for the treatment of related leukemia (right). (**B**) In normal hematopoietic cells (left), MOZ functions as a transcriptional co-activator to potentiate Runx1-dependent gene expression and stimulate cell differentiation. The t(8;16)(p11;p13) translocations (Fig. 5) lead to the production of MOZ-CBP fusion proteins. Unlike wild-type MOZ, these fusion proteins down-modulate Runx1-dependent gene expression and thus lead to leukemogenesis (middle). A similar mechanism may operate with other chromosomal abnormalities with aberrant *MOZ* and *MORF* genes. Inhibitors of the HATs involved may be of therapeutic value for the treatment of related leukemia (right).

DNA replication factor, three DNA metabolic enzymes, a signaling regulator and a cytoskeletal protein (Table 1). In addition, viral proteins are also N^ε-acetylated. Most of these proteins are nuclear, so it will be interesting to examine whether lysine acetylation plays a wider role in the cytoplasm. Intriguingly, this modification has been found in at least three bacterial proteins (Table 1), so it is not just unique to eukaryotic and viral proteins. Consistent with the wide spectrum of substrates, a highly diverse superfamily of LATs has been identified (Table 2). However, enzymes responsible for the acetylation of α-tubulin, Alba and acetyl-CoA synthetase remain elusive. Most known acetyltransferases are catalytic subunits of multiprotein complexes. With distinct sets of subunits, one acetyltransferase can be the catalytic subunit of different complexes, thereby adding another level of diversity. Biochemical and molecular approaches have been and will continue to be fruitful in analyzing the function and regulation of acetyltransferase complexes (6). To understand how lysine acetylation regulates different cellular processes *in vivo*, genetic analysis has been invaluable to distinguish between functional differences of homologous HATs. Gene targeting in mice has revealed that

GCN5L but not PCAF is essential in early embryonic development and that p300 and CBP play distinct roles in hematopoeisis (228,230,252,253). Therefore, such an approach shall continue to yield novel insights into the biological function as well as the spatial and temporal regulation of these and other LATs.

As for molecular mechanisms by which lysine acetylation exerts its effects, one major advance made in the past few years is the discovery that bromodomains are able to recognize acetylated lysine residues (210–216). Many proteins possess such modules (254,255), so one interesting question is whether all bromodomains have such an ability. If so, one major challenge would be to determine the binding specificity of different bromodomains. Degenerate peptide libraries have been successfully used to determine the binding specificity of structural modules involved in cytoplasmic signaling (256). Similar strategies should be valuable for establishing the binding specificity of different chromodomains and understanding their functions in recognizing specific acetylation signals.

The genes for CBP, p300, MOZ and MORF are rearranged by leukemia-associated chromosomal abnormalities (Fig. 5). Some of the resulting fusion proteins have been shown to be leukemogenic (118,161,248). TIP60 has been implicated in the development of prostate cancer (223) and it also interacts with and modulates the function of the cytoplasmic domain of APP, an important regulator of Alzheimer's disease (154,156–158). Expanded polyglutamine tracks, a root cause of Huntington and other polyglutamine diseases, target the acetyltransferase activity of CBP (257–260). In addition, lysine acetylation affects the important roles that various proteins play in other human diseases (Tables 1 and 2). For example, acetylation of HIV Tat is an essential regulatory step for virus production. Therefore, LATs play important roles in the pathogenesis of leukemia (Figs 5 and 6) and other diseases.

Small molecule inhibitors and activators of histone deacetylases have been extensively explored for the treatment of cancer and other human diseases (17,261,262). The direct involvement of LATs in leukemia and other diseases suggests that small molecules able to modulate their enzymatic activities should be of therapeutic potential. In contrast to histone deacetylase inhibitors, only a few small molecules have been shown to modulate the activity of HATs (263–265). Model organisms such as *S.cerevisiae* possess various HAT orthologs (Figs 1 and 2) and may be used to screen for cell-permeable compounds using similar assays to those described for histone deacetylases (266,267). The resulting compounds will yield lead structures for further optimization with iterative rounds of structure-based molecular design and chemical synthesis. Therefore, studies of the fundamental process of lysine acetylation will not only yield important further insights into how post-translational modifications regulate various cellular processes, but also shed new light on the development of novel therapeutic means for the treatment of leukemia and other human diseases.

ACKNOWLEDGEMENTS

REFERENCES

1. Kouzarides,T. (2000) Acetylation: a regulatory modification to rival phosphorylation? *EMBO J.*, **19**, 1176–1179.
2. Strahl,B.D. and Allis,C.D. (2000) The language of covalent histone modifications. *Nature*, **403**, 41–45.
3. Berger,S.L. (2001) An embarrassment of niches: the many covalent modifications of histones in transcriptional regulation. *Oncogene*, **20**, 3007–3013.
4. Roth,S.Y., Denu,J.M. and Allis,C.D. (2001) Histone acetyltransferases. *Annu. Rev. Biochem.*, **70**, 81–120.
5. Turner,B.M. (2002) Cellular memory and the histone code. *Cell*, **111**, 285–291.
6. Carrozza,M.J., Utley,R.T., Workman,J.L. and Cote,J. (2003) The diverse functions of histone acetyltransferase complexes. *Trends Genet.*, **19**, 321–329.
7. Kurdistani,S.K. and Grunstein,M. (2003) Histone acetylation and deacetylation in yeast. *Nature Rev. Mol. Cell Biol.*, **4**, 276–284.
8. Bell,S.D., Botting,C.H., Wardleworth,B.N., Jackson,S.P. and White,M.F. (2002) The interaction of Alba, a conserved archaeal chromatin protein, with Sir2 and its regulation by acetylation. *Science*, **296**, 148–151.
9. Zhao,K., Chai,X. and Marmorstein,R. (2003) Structure of a Sir2 substrate, Alba, reveals a mechanism for deacetylation-induced enhancement of DNA binding. *J. Biol. Chem.*, **278**, 26071–26077.
10. Starai,V.J., Celic,I., Cole,R.N., Boeke,J.D. and Escalante-Semerena,J.C. (2002) Sir2-dependent activation of acetyl-CoA synthetase by deacetylation of active lysine. *Science*, **298**, 2390–2392.
11. Starai,V.J., Takahashi,H., Boeke,J.D. and Escalante-Semerena,J.C. (2003) Short-chain fatty acid activation by acyl-coenzyme A synthetases requires SIR2 protein function in *Salmonella enterica* and *Saccharomyces cerevisiae*. *Genetics*, **163**, 545–555.
12. Polevoda,B. and Sherman,F. (2000) N$^\alpha$-terminal acetylation of eukaryotic proteins. *J. Biol. Chem.*, **275**, 36479–36482.
13. Brownell,J.E., Zhou,J., Ranalli,T., Kobayashi,R., Edmondson,D.G., Roth,S.Y. and Allis,C.D. (1996) *Tetrahymena* histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. *Cell*, **84**, 843–851.
14. Taunton,J., Hassig,C.A. and Schreiber,S.L. (1996) A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. *Science*, **272**, 408–411.
15. Khochbin,S., Verdel,A., Lemercier,C. and Seigneurin-Berny,D. (2001) Functional significance of histone deacetylase diversity. *Curr. Opin. Genet. Dev.*, **11**, 162–166.
16. Gray,S.G. and Ekstrom,T.J. (2001) The human histone deacetylase family. *Exp. Cell Res.*, **262**, 75–83.
17. Grozinger,C.M. and Schreiber,S.L. (2002) Deacetylase enzymes: biological functions and the use of small-molecule inhibitors. *Chem. Biol.*, **9**, 3–16.
18. Yang,X.J. and Seto,E. (2003) Collaborative spirit of histone deacetylases in regulating chromatin structure and gene expression. *Curr. Opin. Genet. Dev.*, **13**, 143–153.
19. Verdin,E., Dequiedt,F. and Kasler,H.G. (2003) Class II histone deacetylases: versatile regulators. *Trends Genet.*, **19**, 286–293.
20. Sterner,D.E. and Berger,S.L. (2000) Acetylation of histones and transcription-related factors. *Microbiol. Mol. Biol. Rev.*, **64**, 435–459.
21. Nakatani,Y. (2001) Histone acetylases—versatile players. *Genes Cell*, **6**, 79–86.
22. Utley,R.T. and Cote,J. (2002) The MYST family of histone acetyltransferases. *Curr. Top. Microbiol. Immunol.*, **274**, 203–236.
23. Kouzarides,T. (2000) Acetylation: a regulatory modification to rival phosphorylation? *EMBO J.*, **19**, 1176–1179.
24. Takei,Y., Swietlik,M., Tanoue,A., Tsujimoto,G., Kouzarides,T. and Laskey,R. (2001) MCM3AP, a novel acetyltransferase that acetylates replication protein MCM3. *EMBO Rep.*, **2**, 119–123.
25. Ivanov,D., Schleiffer,A., Eisenhaber,F., Mechtler,K., Haering,C.H. and Nasmyth,K. (2002) Eco1 is a novel acetyltransferase that can acetylate proteins involved in cohesion. *Curr. Biol.*, **12**, 323–328.
26. Choi,C.H., Hiromura,M. and Usheva,A. (2003) Transcription factor IIB acetylates itself to regulate transcription. *Nature*, **424**, 965–969.
27. Jeong,J.W., Bae,M.K., Ahn,M.Y., Kim,S.H., Sohn,T.K., Bae,M.H., Yoo,M.A., Song,E.J., Lee,K.J. and Kim,K.W. (2003) Regulation and destabilization of HIF-1alpha by ARD1-mediated acetylation. *Cell*, **111**, 709–720.

28. Allfrey,V., Faulkner,R.M. and Mirsky,A.E. (1964) Acetylation and methylation of histones and their possible role in the regulation of RNA synthesis. *Proc. Natl Acad. Sci. USA*, **51**, 786–794.

29. Vidali,G., Gershey,E. and Allfrey,V.G. (1968) Chemical studies of histone acetylation. The distribution of epsilon-N-acetyllysine in calf thymus histones. *J. Biol. Chem.*, **243**, 6361–6366.

30. DeLange,R.J., Fambrough,D.M., Smith,E.L. and Bonner,J. (1969) Calf and pea histone IV. II. The complete amino acid sequence of calf thymus histone IV: presence of epsilon-N-acetyllysine. *J. Biol. Chem.*, **244**, 319–234.

31. Doenecke,D. and Gallwitz,D. (1982) Acetylation of histones in nucleosomes. *Mol. Cell. Biochem.*, **44**, 113–128.

32. Sterner,R., Vidali,G. and Allfrey,V.G. (1979) Studies of acetylation and deacetylation in high mobility group proteins. Identification of the sites of acetylation in HMG-1. *J. Biol. Chem.*, **254**, 11577–11583.

33. LeDizet,M. and Piperno,G. (1987) Identification of an acetylation site of *Chlamydomonas* α-tubulin. *Proc. Natl Acad. Sci. USA*, **84**, 5720–5724.

34. Gu,W. and Roeder,R.G. (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. *Cell*, **90**, 595–606.

35. Imhof,A., Yang,X.-J., Ogryzko,V.V., Nakatani,Y., Wolffe,A.P. and Ge,H. (1997) Acetylation of general transcription factors by histone acetyltransferases. *Curr. Biol.*, **7**, 689–692.

36. Chen,H., Tini,M. and Evans,R.M. (2001) HATs on and beyond chromatin. *Curr. Opin. Cell Biol.*, **13**, 218–224.

37. Chen,H., Lin,R.J., Xie,V.V., Wilpitz,D. and Evans,R.M. (1999) Regulation of hormone-induced histone hyperacetylation and gene activation via acetylation of an acetylase. *Cell*, **98**, 675–686.

38. Vo,N., Fjeld,C. and Goodman,R.H. (2001) Acetylation of nuclear hormone receptor-interacting protein RIP140 regulates binding of the transcriptional corepressor CtBP. *Mol. Cell. Biol.*, **21**, 6181–6188.

39. Chan,H.M., Krstic-Demonacos,M., Smith,L., Demonacos,C. and La Thangue,N.B. (2001) Acetylation control of the retinoblastoma tumour-suppressor protein. *Nature Cell Biol.*, **3**, 667–674.

40. Wolf,D., Rodova,M., Miska,E.A., Calvet,J.P. and Kouzarides,T. (2002) Acetylation of beta-catenin by CREB-binding protein (CBP). *J. Biol. Chem.*, **277**, 25562–25567.

41. Spilianakis,C., Papamatheakis,J. and Kretsovali,A. (2000) Acetylation by PCAF enhances CIITA nuclear accumulation and transactivation of major histocompatibility complex class II genes. *Mol. Cell. Biol.*, **20**, 8489–8498.

42. Herrera,J.E., Bergel,M., Yang,X.J., Nakatani,Y. and Bustin,M. (1997) The histone acetyltransferase activity of human GCN5 and PCAF is stabilized by coenzymes. *J. Biol. Chem.*, **272**, 27253–27258.

43. Ogryzko,V.V., Schiltz,R.L., Russanova,V., Howard,B.H. and Nakatani,Y. (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. *Cell*, **87**, 953–959.

44. Bannister,A.J. and Kouzarides,T. (1996) The CBP co-activator is a histone acetyltransferase. *Nature*, **384**, 641–643.

45. Champagne,N., Bertos,N.R., Pelletier,N., Wang,A.H., Vezmar,M., Yang,Y., Heng,H.H. and Yang,X.J. (1999) Identification of a human histone acetyltransferase related to monocytic leukemia zinc finger protein. *J. Biol. Chem.*, **274**, 28528–28536.

46. Santos-Rosa,H., Valls,E., Kouzarides,T. and Martinez-Balbas,M. (2003) Mechanisms of P/CAF auto-acetylation. *Nucleic Acids Res.*, **31**, 4285–4292.

47. Bourachot,B., Yaniv,M. and Muchardt,C. (2003) Growth inhibition by the mammalian SWI–SNF subunit Brm is regulated by acetylation. *EMBO J.*, **22**, 6505–6515.

48. Hasan,S., Stucki,M., Hassa,P.O., Imhof,R., Gehrig,P., Hunziker,P., Hubscher,U. and Hottiger,M.O. (2001) Regulation of human flap endonuclease-1 activity by acetylation through the transcriptional coactivator p300. *Mol. Cell*, **7**, 1221–1231.

49. Tini,M., Benecke,A., Um,S.J., Torchia,J., Evans,R.M. and Chambon,P. (2002) Association of CBP/p300 acetylase and thymine DNA glycosylase links DNA repair and transcription. *Mol. Cell*, **9**, 265–277.

50. Blander,G., Zalle,N., Daniely,Y., Taplick,J., Gray,M.D. and Oren,M. (2002) DNA damage-induced translocation of the Werner helicase is regulated by acetylation. *J. Biol. Chem.*, **277**, 50934–50940.

51. Gronroos,E., Hellman,U., Heldin,C.H. and Ericsson,J. (2002) Control of Smad7 stability by competition between acetylation and ubiquitination. *Mol. Cell*, **10**, 483–493.

52. Kiernan,R.E., Vanhulle,C., Schiltz,L., Adam,E., Xiao,H., Maudoux,F., Calomme,C., Burny,A., Nakatani,Y., Jeang,K.T. *et al*. (1999) HIV-1 tat

53. Ott,M., Schnolzer,M., Garnica,J., Fischle,W., Emiliani,S., Rackwitz,H.R. and Verdin,E. (1999) Acetylation of the HIV-1 Tat protein by p300 is important for its transcriptional activity. *Curr. Biol.*, **9**, 1489–1492.

54. Zhang,Q., Yao,H., Vo,N. and Goodman,R.H. (2000) Acetylation of adenovirus E1A regulates binding of the transcriptional corepressor CtBP. *Proc. Natl Acad. Sci. USA*, **97**, 14323–14328.

55. Xie,A.Y., Bermudez,V.P. and Folk,W.R. (2002) Stimulation of DNA replication from the polyomavirus origin by PCAF and GCN5 acetyltransferases: acetylation of large T antigen. *Mol. Cell. Biol.*, **22**, 7907–7918.

56. Ramakrishnan,R., Schuster,M. and Bourret,R.B. (1998) Acetylation at Lys-92 enhances signaling by the chemotaxis response regulator protein CheY. *Proc. Natl Acad. Sci. USA*, **95**, 4918–4923.

57. Barak,R. and Eisenbach,M. (2001) Acetylation of the response regulator, CheY, is involved in bacterial chemotaxis. *Mol. Microbiol.*, **40**, 731–743.

58. Kleff,S., Andrulis,E.D., Anderson,C.W. and Sternglanz,R. (1995) Identification of a gene encoding a yeast histone H4 acetyltransferase. *J. Biol. Chem.*, **270**, 24674–24677.

59. Kelly,T.J., Qin,S., Gottschling,D.E. and Parthun,M.R. (2000) Type B histone acetyltransferase Hat1p participates in telomeric silencing. *Mol. Cell. Biol.*, **20**, 7051–7058.

60. Yang,X.J., Ogryzko,V.V., Nishikawa,J., Howard,B.H. and Nakatani,Y. (1996) A p300/CBP-associated factor that competes with the adenoviral oncoprotein E1A. *Nature*, **382**, 319–324.

61. Mizzen,C.A., Yang,X.J., Kokubo,T., Brownell,J.E., Bannister,A.J., Owen-Hughes,T., Workman,J., Wang,L., Berger,S.L., Kouzarides,T. *et al*. (1996) The TAF(II)250 subunit of TFIID has histone acetyltransferase activity. *Cell*, **87**, 1261–1270.

62. Spencer,T.E., Jenster,G., Burcin,M.M., Allis,C.D., Zhou,J., Mizzen,C.A., Mckenna,N.J., Onate,S.A., Tsai,S.Y., Tsai,M.-J. *et al*. (1997) Steroid receptor coactivator-1 is a histone acetyltransferase. *Nature*, **389**, 194–197.

63. Chen,H., Lin,R.J., Schiltz,R.L., Chakravati,D., Nash,A., Nagy,L., Privalsky,M.L., Nakatani,Y. and Evans,R.M. (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. *Cell*, **90**, 569–580.

64. Raval,A., Howcroft,K., Weissman,J.D., Kirshner,S., Zhu,X.S., Yokoyama,K., Ting,J. and Singer,D. (2001) Transcriptional coactivator, CIITA, is an acetyltransferase that bypasses a promoter requirment for TAFII250. *Mol. Cell*, **7**, 105–115.

65. Kawasaki,H., Schiltz,L., Chiu,R., Itakura,K., Taira,K., Nakatani,Y. and Yokoyama,K.K. (2000) ATF-2 has intrinsic histone acetyltransferase activity which is modulated by phosphorylation. *Nature*, **405**, 195–200.

66. Lorch,Y., Beve,J., Gustafsson,C.M., Myers,L.C. and Kornberg,R.D. (2000) Mediator–nucleosome interaction. *Mol. Cell*, **6**, 197–201.

67. Hsieh,Y.J., Kundu,T.K., Wang,Z., Kovelman,R. and Roeder,R.G. (1999) The TFIIIC90 subunit of TFIIIC interacts with multiple components of the RNA polymerase III machinery and contains a histone-specific acetyltransferase activity. *Mol. Cell. Biol.*, **19**, 7697–7704.

68. Wittschieben,B.O., Otero,G., de Bizemont,T., Fellows,J., Erdjument-Bromage,H., Ohba,R., Li,Y., Allis,C.D., Tempst,P. and Svejstrup,J.Q. (1999) A novel histone acetyltransferase is an integral subunit of elongating RNA polymerase II holoenzyme. *Mol. Cell*, **4**, 123–128.

69. Angus-Hill,M., Dutnall,R.N., Tafrov,S.T., Sternglanz,R. and Ramakrishnan,V. (1999) Crystal structure of the histone acetyltransferase Hpa2: a tetrameric member of the Gcn5-related N-acetyltransferase superfamily. *J. Mol. Biol.*, **294**, 1311–1325.

70. Lahn,B.T., Tang,Z.L., Zhou,J., Barndt,R.J., Parvinen,M., Allis,C.D. and Page,D.C. (2002) Previously uncharacterized histone acetyltransferases implicated in mammalian spermatogenesis. *Proc. Natl Acad. Sci. USA*, **99**, 9707–8712.

71. Jacobson,S. and Pillus,L. (1999) Modifying chromatin and concepts of cancer. *Curr. Opin. Genet. Dev.*, **9**, 175–184.

72. Georgakopoulos,T. and Thireos,G. (1992) Two distinct yeast transcriptional activators require the function of the GCN5 protein to promote normal levels of transcription. *EMBO J.*, **11**, 4145–4152.

73. Wang,L., Mizzen,C., Ying,C., Candau,R., Barlev,N., Brownell,J., Allis,C.D. and Berger,S.L. (1997) Histone acetyltransferase activity is

conserved between yeast and human GCN5 and is required for complementation of growth and transcriptional activation. *Mol. Cell. Biol.*, **17**, 519–527.

74. Smith,E.R., Belote,J.M., Schiltz,R.L., Yang,X.J., Moore,P.A., Berger,S.L., Nakatani,Y. and Allis,C.D. (1998) Cloning of *Drosophila* GCN5: conserved features among metazoan GCN5 family members. *Nucleic Acids Res.*, **26**, 2948–2954.

75. Xu,W., Edmondson,D.G. and Roth,S.Y. (1998) Mammalian GCN5 and P/CAF acetyltransferases have homologous amino-terminal domains important for recognition of nucleosomal substrates. *Mol. Cell. Biol.*, **18**, 5655–5669.

76. Maciel,R.M., Silva Dutra,D.L., Rumjanek,F.D., Juliano,L., Juliano,M.A. and Fantappie,M.R. (2004) *Schistosoma mansoni* histone acetyltransferase GCN5: linking histone acetylation to gene activation. *Mol. Biochem. Parasitol.*, **133**, 131–135.

77. Giordano,A. and Avantaggiati,M.L. (1999) p300 and CBP: partners for life and death. *J. Cell. Physiol.*, **181**, 218–230.

78. Goodman,R.H. and Smolik,S. (2000) CBP/p300 in cell growth, transformation and development. *Genes Dev.*, **14**, 1553–1577.

79. Chan,H.M. and La Thangue,N.B. (2001) p300/CBP proteins: HATs for transcriptional bridges and scaffolds. *J. Cell Sci.*, **114**, 2363–2373.

80. Bordoli,L., Netsch,M., Luthi,U., Lutz,W. and Eckner,R. (2001) Plant orthologs of p300/CBP: conservation of a core domain in metazoan p300/CBP acetyltransferase-related proteins. *Nucleic Acids Res.*, **29**, 589–597.

81. Pandey,R., Muller,A., Napoli,C.A., Selinger,D.A., Pikaard,C.S., Richards,E.J., Bender,J., Mount,D.W. and Jorgensen,R.A. (2002) Analysis of histone acetyltransferase and histone deacetylase families of *Arabidopsis thaliana* suggests functional diversification of chromatin modification among multicellular eukaryotes. *Nucleic Acids Res.*, **30**, 5036–5055.

82. Neuwald,A.F. and Landsman,D. (1997) GCN5-related histone N-acetyltransferases belong to a diverse superfamily that includes the yeast SPT10 protein. *Trends Biochem. Sci.*, **22**, 154–155.

83. Borrow,J., Stanton,V.P.,Jr, Andresen,J.M., Becher,R., Behm,F.G., Chaganti,R.S., Civin,C.I., Disteche,C., Dube,I., Frischauf,A.M. *et al.* (1996) The translocation t(8;16)(p11;p13) of acute myeloid leukaemia fuses a putative acetyltransferase to the CREB-binding protein. *Nature Genet.*, **14**, 33–41.

84. Reifsnyder,C., Lowell,J., Clarke,A. and Pillus,L. (1996) Yeast SAS silencing genes and human genes associated with AML and HIV-1 Tat interactions are homologous with acetyltransferases. *Nature Genet.*, **14**, 42–49.

85. Grant,P.A., Duggan,L., Cote,J., Roberts,S.M., Brownell,J.E., Candau,R., Ohba,R., Owen-Hughes,T., Allis,C.D., Winston,F. *et al.* (1997) Yeast GCN5 functions in two multisubunit complexes to acetylate nucleosomal histones: characterization of an Ada complex and the SAGA (Spt/Ada) complex. *Genes Dev.*, **11**, 1640–1650.

86. Ogryzko,V.V., Kotani,T., Zhang,X., Schlitz,R.L., Howard,T., Yang,X.J., Howard,B.H., Qin,J. and Nakatani,Y. (1998) Histone-like TAFs within the PCAF histone acetylase complex. *Cell*, **94**, 35–44.

87. Sendra,R., Tse,C. and Hansen,J.C. (2000) The yeast histone acetyltransferase A2 complex, but not free Gcn5p, binds stably to nucleosomal arrays. *J. Biol. Chem.*, **275**, 24928–24934.

88. Boudreault,A.A., Cronier,D., Selleck,W., Lacoste,N., Utley,R.T., Allard,S., Savard,J., Lane,W.S., Tan,S. and Cote,J. (2003) Yeast enhancer of polycomb defines global Esa1-dependent acetylation of chromatin. *Genes Dev.*, **17**, 1415–1428.

89. Brand,M., Yamamoto,K., Staub,A. and Tora,L. (1999) Identification of TATA-binding protein-free TAFII-containing complex subunits suggests a role in nucleosome acetylation and signal transduction. *J. Biol. Chem.*, **274**, 18285–18289.

90. Martinez,E., Palhan,V.B., Tjernberg,A., Lymar,E.S., Gamper,A.M., Kundu,T.K., Chait,B.T. and Roeder,R.G. (2001) Human STAGA complex is a chromatin-acetylating transcription coactivator that interacts with pre-mRNA splicing and DNA damage-binding factors *in vivo*. *Mol. Cell. Biol.*, **21**, 6782–6795.

91. Yanagisawa,J., Kitagawa,H., Yanagida,M., Wada,O., Ogawa,S., Nakagomi,M., Oishi,H., Yamamoto,Y., Nagasawa,H., McMahon,S.B. *et al.* (2002) Nuclear receptor function requires a TFTC-type histone acetyl transferase complex. *Mol. Cell*, **9**, 553–562.

92. Grant,P.A., Schieltz,D., Pray-Grant,M.G., Yates,J.R. and Workman,J.L. (1998) The ATM-related cofactor Tra1 is a component of the purified SAGA complex. *Mol. Cell*, **2**, 863–867.

93. Saleh,A., Schieltz,D., Ting,N., McMahon,S.B., Litchfield,D.W., Yates,J.R., Lees-Miller,S.P., Cole,M.D. and Brandl,C.J. (1998) Tra1p is a component of the yeast Ada.Spt transcriptional regulatory complexes. *J. Biol. Chem.*, **273**, 26559–26565.

94. Allard,S., Utley,R.T., Savard,J., Clarke,A., Grant,P., Brandl,C.J., Pillus,L., Workman,J.L. and Cote,J. (1999) NuA4, an essential transcription adaptor/histone H4 acetyltransferase complex containing Esa1p and the ATM-related cofactor Tra1p. *EMBO J.*, **18**, 5108–5119.

95. Sterner,D.E., Belotserkovskaya,R. and Berger,S.L. (2002) ALSA, a variant of yeast SAGA, contains truncated Spt7, which correlates with activated transcription. *Proc. Natl Acad. Sci. USA*, **99**, 11622–11627.

96. Pray-Grant,M.G., Schieltz,D., McMahon,S.J., Wood,J.M., Kennedy,E.L., Cook,R.G., Workman,J.L., Yates,J.R.,3rd and Grant,P.A. (2002) The novel SLIK histone acetyltransferase complex functions in the yeast retrograde response pathway. *Mol. Cell. Biol.*, **22**, 8774–8786.

97. Henry,K.W., Wyce,A., Lo,W.S., Duggan,L.J., Emre,N.C., Kao,C.F., Pillus,L., Shilatifard,A., Osley,M.A. and Berger,S.L. (2003) Transcriptional activation via sequential histone H2B ubiquitylation and deubiquitylation, mediated by SAGA-associated Ubp8. *Genes Dev.*, **17**, 2648–2663.

98. Daniel,J.A., Torok,M.S., Sun,Z.W., Schieltz,D., Allis,C.D., Yates,J.R. and Grant,P.A. (2003) Deubiquitination of histone H2B by a yeast acetyltransferase complex regulates transcription. *J. Biol. Chem.*, **279**, 1867–1871.

99. Zhang,Y. (2003) Transcriptional regulation by histone ubiquitination and deubiquitination. *Genes Dev.*, **17**, 2733–2740.

100. Fuks,F., Milner,J. and Kouzarides,T. (1998) BRCA2 associates with acetyltransferase activity when bound to P/CAF. *Oncogene*, **17**, 2531–2534.

101. Sutton,A., Shia,W.J., Band,D., Kaufman,P.D., Osada,S., Workman,J.L. and Sternglanz,R. (2003) Sas4 and Sas5 are required for the histone acetyltransferase activity of Sas2 in the SAS complex. *J. Biol. Chem.*, **278**, 16887–16892.

102. Kimura,A., Umehara,T. and Horikoshi,M. (2002) Chromosomal gradient of histone acetylation established by Sas2p and Sir2p functions as a shield against gene silencing. *Nature Genet.*, **32**, 370–377.

103. Suka,N., Luo,K. and Grunstein,M. (2002) Sir2p and Sas2p opposingly regulate acetylation of yeast histone H4 lysine16 and spreading of heterochromatin. *Nature Genet.*, **32**, 378–383.

104. Takechi,S. and Nakayama,T. (1999) Sas3 is a histone acetyltransferase and requires a zinc finger motif. *Biochem. Biophys. Res. Commun.*, **266**, 405–410.

105. Kamine,J., Elangovan,B., Subramanian,T., Coleman,D. and Chinnadurai,G. (1996) Identification of a cellular protein that specifically interacts with the essential cysteine region of the HIV-1 Tat transactivator. *Virology*, **216**, 357–366.

106. Yamamoto,T. and Horikoshi,M. (1997) Novel substrate specificity of the histone acetyltransferase activity of HIV-1-Tat interactive protein Tip60. *J. Biol. Chem.*, **272**, 30595–30598.

107. Ran,Q. and Pereira-Smith,O.M. (2000) Identification of an alternatively spliced form of the Tat interactive protein (Tip60), Tip60beta. *Gene*, **258**, 141–146.

108. Smith,E.R., Eisen,A., Gu,W., Sattah,M., Pannuti,A., Zhou,J., Cook,R.G., Lucchesi,J.C. and Allis,C.D. (1998) ESA1 is a histone acetyltransferase that is essential for growth in yeast. *Proc. Natl Acad. Sci. USA*, **95**, 3561–3565.

109. Clarke,A.S., Lowell,J.E., Jacobson,S.J. and Pillus,L. (1999) Esa1p is an essential histone acetyltransferase required for cell cycle progression. *Mol. Cell. Biol.*, **19**, 2515–2526.

110. Hilfiker,A., Hilfiker-Kleiner,D., Pannuti,A. and Lucchesi,J.C. (1997) MOF, a putative acetyl transferase gene related to the Tip60 and MOZ human genes and to the SAS genes of yeast, is required for dosage compensation in *Drosophila*. *EMBO J.*, **16**, 2054–2060.

111. Akhtar,A. and Becker,P.B. (2000) Activation of transcription through histone H4 acetylation by MOF, an acetyltransferase essential for dosage compensation in *Drosophila*. *Mol. Cell*, **5**, 367–375.

112. Scott,E.K., Lee,T. and Luo,L. (2001) Enok encodes a *Drosophila* putative histone acetyltransferase required for mushroom body neuroblast proliferation. *Curr. Biol.*, **11**, 99–104.

113. Grienenberger,A., Miotto,B., Sagnier,T., Cavalli,G., Schramke,V., Geli,V., Mariol,M.C., Berenger,H., Graba,Y. and Pradel,J. (2002) The MYST domain acetyltransferase Chameau functions in epigenetic mechanisms of transcriptional repression. *Curr. Biol.*, **12**, 762–766.

114. Iizuka,M. and Stillman,B. (1999) Histone acetyltransferase HBO1 interacts with the ORC1 subunit of the human initiator protein. *J. Biol. Chem.*, **274**, 23027–23034.

115. Yan,Y., Harper,S., Speicher,D.W. and Marmorstein,R. (2002) The catalytic mechanism of the ESA1 histone acetyltransferase involves a self-acetylated intermediate. *Nature Struct. Biol.*, **9**, 862–869.

116. Yan,Y., Barlev,N.A., Haley,R.H., Berger,S.L. and Marmorstein,R. (2000) Crystal structure of yeast Esa1 suggests a unified mechanism for catalysis and substrate binding by histone acetyltransferases. *Mol. Cell*, **6**, 1195–1205.

117. Akhtar,A. and Becker,P.B. (2001) The histone H4 acetyltransferase MOF uses a C2HC zinc finger for substrate recognition. *EMBO Rep.*, **2**, 113–118.

118. Deguchi,K., Ayton,P.M., Carapeti,M., Kutok,J.L., Snyder,C.S., Williams,I.R., Cross,N.C., Glass,C.K., Cleary,M.L. and Gilliland,D.G. (2003) MOZ-TIF2-induced acute myeloid leukemia requires the MOZ nucleosome binding motif and TIF2-mediated recruitment of CBP. *Cancer Cell*, **3**, 259–271.

119. Nordentoft,I. and Jorgensen,P. (2003) The acetyltransferase 60 kDa trans-acting regulatory protein of HIV type 1-interacting protein (Tip60) interacts with the translocation E26 transforming-specific leukaemia gene (TEL) and functions as a transcriptional co-repressor. *Biochem. J.*, **374**, 165–173.

120. Jones,D.O., Cowell,I.G. and Singh,P.B. (2000) Mammalian chromodomain proteins: their role in genome organisation and expression. *Bioessays*, **22**, 124–137.

121. Akhtar,A., Zink,D. and Becker,P.B. (2000) Chromodomains are protein–RNA interaction modules. *Nature*, **407**, 405–409.

122. Bannister,A.J., Zegerman,P., Partridge,J.F., Miska,E.A., Thomas,J.O., Allshire,R.C. and Kouzarides,T. (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. *Nature*, **410**, 120–124.

123. Nakayama,J., Rice,J.C., Strahl,B.D., Allis,C.D. and Grewal,S.I. (2001) Role of histone H3 lysine 9 methylation in epigenetic control of heterochromatin assembly. *Science*, **292**, 110–113.

124. Aasland,R., Gibson,T.J. and Stewart,A.F. (1995) The PHD finger: implications for chromatin-mediated transcriptional regulation. *Trends Biochem. Sci.*, **20**, 56–59.

125. Saha,V., Chaplin,T., Gregorini,A., Ayton,P. and Young,B.D. (1995) The leukemia-associated-protein (LAP) domain, a cysteine-rich motif, is present in a wide range of proteins, including MLL, AF10 and MLLT6 proteins. *Proc. Natl Acad. Sci. USA*, **92**, 9737–9741.

126. Ito,T., Levenstein,M.E., Fyodorov,D.V., Kutach,A.K., Kobayashi,R. and Kadonaga,J.T. (1999) ACF consists of two subunits, Acf1 and ISWI, that function cooperatively in the ATP-dependent catalysis of chromatin assembly. *Genes Dev.*, **13**, 1529–1539.

127. Capili,A.D., Schultz,D.C., Rauscher,F.J. and Borden,K.L.B. (2001) Solution structure of the PHD domain of the KAP-1 corepressor: structural determinants for PHD, RING and LIM zinc binding domains. *EMBO J.*, **20**, 165–177.

128. Gibbons,R.J., Pellagatti,A., Garrick,D., Wood,W.G., Malik,N., Ayyub,H., Langford,C., Boultwood,J., Wainscoat,J.S. and Higgs,D.R. (2003) Identification of acquired somatic mutations in the gene encoding chromatin-remodeling factor ATRX in the α-thalassemia myelodysplasia syndrome (ATMDS). *Nature Genet.*, **34**, 446–449.

129. Coscoy,L. and Ganem,D. (2003) PHD domains and E3 ubiquitin ligases: viruses make the connection. *Trends Cell Biol.*, **13**, 7–12.

130. Scheel,H. and Hofmann,K. (2003) No evidence for PHD fingers as ubiquitin ligases. *Trends Cell Biol.*, **13**, 285–287.

131. Gozani,O., Karuman,P., Jones,D.R., Ivanov,D., Cha,J., Lugovskoy,A.A., Baird,C.L., Zhu,H., Field,S.J., Lessnick,S.L. *et al.* (2003) The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, **114**, 99–111.

132. Ramakrishnan,V., Finch,J.T., Graziano,V., Lee,P.L. and Sweet,R.M. (1993) Crystal structure of globular domain of histone H5 and its implications for nucleosome binding. *Nature*, **362**, 219–223.

133. Carter,G.J. and Holde,K.V. (1998) Self-association of linker histone H5 and of its globular domain: evidence for specific self-contacts. *Biochemistry*, **37**, 12477–12488.

134. Champagne,N., Pelletier,N. and Yang,X.J. (2001) The monocytic leukemia zinc finger protein MOZ is a histone acetyltransferase. *Oncogene*, **20**, 404–409.

135. Galarneau,L., Nourani,A., Boudreault,A.A., Zhang,Y., Heliot,L., Allard,S., Savard,J., Lane,W.S., Stillman,D.J. and Cote,J. (2000) Multiple links between the NuA4 histone acetyltransferase complex and epigenetic control of transcription. *Mol. Cell*, **5**, 927–937.

136. Eisen,A., Utley,R.T., Nourani,A., Allard,S., Schmidt,P., Lane,W.S., Lucchesi,J.C. and Cote,J. (2000) The yeast NuA4 and *Drosophila* MSL complexes contain homologous subunits important for transcriptional regulation. *J. Biol. Chem.*, **276**, 3484–3491.

137. John,S., Howe,L., Tafrov,S.T., Grant,P.A., Sternglanz,R. and Workman,J.L. (2000) The something about silencing protein, Sas3, is the catalytic subunit of NuA3, a yTAF(II)30-containing HAT complex that interacts with the Spt16 subunit of the yeast CP(Cdc68/Pob3)-FACT complex. *Genes Dev.*, **14**, 1196–1208.

138. Osada,S., Sutton,A., Muster,N., Brown,C.E., Yates,J.R.,III, Sternglanz,R. and Workman,J.L. (2001) The yeast SAS (something about silencing) protein complex contains a MYST-type putative acetyltransferase and functions with chromatin assembly factor ASF1. *Genes Dev.*, **15**, 3155–3168.

139. Meijsing,S.H. and Ehrenhofer-Murray,A.E. (2001) The silencing complex SAS-I links histone acetylation to the assembly of repressed chromatin by CAF-I and Asf1 in *Saccharomyces cerevisiae*. *Genes Dev.*, **15**, 3169–3182.

140. Pannuti,A. and Lucchesi,J.C. (2000) Recycling to remodel: evolution of dosage-compensation complexes. *Curr. Opin. Genet. Dev.*, **10**, 644–650.

141. Ikura,T., Ogryzko,V.V., Grigoriev,M., Groisman,R., Wang,J., Horikoshi,M., Scully,R., Qin,J. and Nakatani,Y. (2000) Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis. *Cell*, **102**, 463–473.

142. Cai,Y., Jin,J., Tomomori-Sato,C., Sato,S., Sorokina,I., Parmely,T.J., Conaway,R.C. and Conaway,J.W. (2003) Identification of new subunits of the multiprotein mammalian TRRAP/Tip60-containing histone acetyltransferase complex. *J. Biol. Chem.*, **278**, 42733–42736.

143. McMahon,S.B., Buskirk,H.A.V., Dugan,K.A., Copeland,T.D. and Cole,M.D. (1998) The novel ATM-related protein TRRAP is an essential cofactor for the c-Myc and E2F oncoproteins. *Cell*, **94**, 363–374.

144. Vassilev,A., Yamauchi,J., Kotani,T., Prives,C., Avantaggiati,M.L., Qin,J. and Nakatani,Y. (1998) The 400 kDa subunit of the PCAF histone acetylase complex belongs to the ATM superfamily. *Mol. Cell*, **2**, 869–875.

145. Fuchs,M., Gerber,J., Drapkin,R., Sif,S., Ikura,T., Ogryzko,V., Lane,W.S., Nakatani,Y. and Livingston,D.M. (2001) The p400 complex is an essential E1A transformation target. *Cell*, **106**, 297–307.

146. Loewith,R., Meijer,M., Lees-Miller,S.P., Riabowol,K. and Young,D. (2000) Three yeast proteins related to the human candidate tumor suppressor p33(ING1) are associated with histone acetyltransferase activities. *Mol. Cell. Biol.*, **20**, 3807–3816.

147. Feng,X., Hara,Y. and Riabowol,K. (2002) Different HATS of the ING1 gene family. *Trends Cell Biol.*, **12**, 532–538.

148. Bird,A.W., Yu,D.Y., Pray-Grant,M.G., Qiu,Q., Harmon,K.E., Megee,P.C., Grant,P.A., Smith,M.M. and Christman,M.F. (2002) Acetylation of histone H4 by Esa1 is required for DNA double-strand break repair. *Nature*, **419**, 411–415.

149. Reid,J.L., Iyer,V.R., Brown,P.O. and Struhl,K. (2000) Coordinate regulation of yeast ribosomal protein genes is associated with targeted recruitment of Esa1 histone acetylase. *Mol. Cell*, **6**, 1297–1307.

150. Nourani,A., Howe,L., Pray-Grant,M.G., Workman,J.L., Grant,P.A. and Cote,J. (2003) Opposite role of yeast ING family members in p53-dependent transcriptional activation. *J. Biol. Chem.*, **278**, 19171–19175.

151. Xiao,H., Chung,J., Kao,H.Y. and Yang,Y.C. (2003) Tip60 is a co-repressor for STAT3. *J. Biol. Chem.*, **278**, 11197–11204.

152. Brady,M.E., Ozanne,D.M., Gaughan,L., Waite,I., Cook,S., Neal,D.E. and Robson,C.N. (1999) TIP60 is a nuclear hormone receptor coactivator. *J. Biol. Chem.*, **274**, 17599–17604.

153. Gaughan,L., Logan,I.R., Cook,S., Neal,D.E. and Robson,C.N. (2002) Tip60 and histone deacetylase 1 regulate androgen receptor activity through changes to the acetylation status of the receptor. *J. Biol. Chem.*, **277**, 25904–25913.

154. Baek,S.H., Ohgi,K.A., Rose,D.W., Koo,E.H., Glass,C.K. and Rosenfeld,M.G. (2002) Exchange of N-CoR corepressor and Tip60 coactivator complexes links gene expression by NF-kappaB and beta-amyloid precursor protein. *Cell*, **110**, 55–67.

155. Frank,S.R., Parisi,T., Taubert,S., Fernandez,P., Fuchs,M., Chan,H.M., Livingston,D.M. and Amati,B. (2003) MYC recruits the TIP60 histone acetyltransferase complex to chromatin. *EMBO Rep.*, **4**, 575–580.

156. Cao,X. and Sudhof,T.C. (2001) A transcriptively active complex of APP with Fe65 and histone acetyltransferase Tip60. *Science*, **293**, 115–120.

157. Kinoshita,A., Whelan,C.M., Berezovska,O. and Hyman,B.T. (2002) The gamma secretase-generated carboxyl-terminal domain of the amyloid precursor protein induces apoptosis via Tip60 in H4 cells. *J. Biol. Chem.*, **277**, 28530–28536.

158. Scheinfeld,M.H., Matsuda,S. and D'Adamio,L. (2003) JNK-interacting protein-1 promotes transcription of A beta protein precursor but not A beta precursor-like proteins, mechanistically different than Fe65. *Proc. Natl Acad. Sci. USA*, **100**, 1729–1734.

159. Sharma,M., Zarnegar,M., Li,X., Lim,B. and Sun,Z. (2000) Androgen receptor interacts with a novel MYST protein, HBO1. *J. Biol. Chem.*, **275**, 35200–35208.

160. Pardo,P.S., Leung,J.K., Lucchesi,J.C. and Pereira-Smith,O.M. (2002) MRG15, a novel chromodomain protein, is present in two distinct multiprotein complexes involved in transcriptional activation. *J. Biol. Chem.*, **277**, 50860–50866.

161. Kitabayashi,I., Aikawa,Y., Nguyen,L.A., Yokoyama,A. and Ohki,M. (2001) Activation of AML1-mediated transcription by MOZ and inhibition by the MOZ-CBP fusion protein. *EMBO J.*, **20**, 7184–7196.

162. Surapureddi,S., Yu,S., Bu,H., Hashimoto,T., Yeldandi,A.V., Kashireddy,P., Cherkaoui-Malki,M., Qi,C., Zhu,Y.J., Rao,M.S. *et al.* (2002) Identification of a transcriptionally active peroxisome proliferator-activated receptor alpha-interacting cofactor complex in rat liver and characterization of PRIC285 as a coactivator. *Proc. Natl Acad. Sci. USA*, **99**, 11836–11841.

163. Pelletier,N., Champagne,N., Stifani,S. and Yang,X.J. (2002) MOZ and MORF histone acetyltransferases interact with the Runt-domain transcription factor Runx2. *Oncogene*, **21**, 2729–2740.

164. Bristow,C.A. and Shore,P. (2003) Transcriptional regulation of the human MIP-1alpha promoter by RUNX1 and MOZ. *Nucleic Acids Res.*, **31**, 2735–2744.

165. Westendorf,J.J. and Hiebert,S.W. (1999) Mammalian Runt-domain proteins and their roles in hematopoisis, osteogenesis and leukemia. *J. Cell. Biochem.*, (Suppl.) **32/33**, 51–58.

166. Wheeler,J.C., Shigesada,K., Gergen,J.P. and Ito,Y. (2000) Mechanisms of transcriptional regulation by Runt domain proteins. *Semin. Cell Dev. Biol.*, **11**, 369–375.

167. Ducy,P., Schinke,T. and Karsenty,G. (2000) The osteoblast: a sophisticated fibroblast under central surveillance. *Science*, **289**, 1501–1504.

168. Speck,N.A. and Gilliland,D.G. (2002) Core-binding factors in haematopoiesis and leukaemia. *Nature Rev. Cancer*, **2**, 502–513.

169. Thomas,T., Voss,A.K., Chowdhury,K. and Gruss,P. (2000) Querkopf, a MYST family histone acetyltransferase, is required for normal cerebral cortex development. *Development*, **127**, 2537–2548.

170. Perissi,V., Dasen,J.S., Kurokawa,R., Wang,Z., Korzus,E., Rose,D.W., Glass,C.K. and Rosenfeld,M.G. (1999) Factor-specific modulation of CREB-binding protein acetyltransferase activity. *Proc. Natl Acad. Sci. USA*, **96**, 3652–3657.

171. Hamamori,Y., Sartorelli,V., Ogryzko,V., Puri,P.L., Wu,H.Y., Wang,J.Y., Nakatani,Y. and Kedes,L. (1999) Regulation of histone acetyltransferases p300 and PCAF by the bHLH protein twist and adenoviral oncoprotein E1A. *Cell*, **96**, 405–413.

172. Li,M., Damania,B., Alvarez,X., Ogryzko,V., Ozato,K. and Jung,J.U. (2000) Inhibition of p300 histone acetyltransferase by viral interferon regulatory factor. *Mol. Cell. Biol.*, **20**, 8254–8263.

173. Chen,C.J., Deng,Z., Kim,A.Y., Blobel,G.A. and Lieberman,P.M. (2001) Stimulation of CREB binding protein nucleosomal histone acetyltransferase activity by a class of transcriptional activators. *Mol. Cell. Biol.*, **21**, 476–487.

174. Shen,W.F., Krishnan,K., Lawrence,H.J. and Largman,C. (2001) The HOX homeodomain proteins block CBP histone acetyltransferase activity. *Mol. Cell. Biol.*, **21**, 7509–7522.

175. Hong,W., Kim,A.Y., Ky,S., Rakowski,C., Seo,S.B., Chakravarti,D., Atchison,M. and Blobel,G.A. (2002) Inhibition of CBP-mediated protein acetylation by the Ets family oncoprotein PU.1. *Mol. Cell. Biol.*, **22**, 3729–3743.

176. Zhao,F., McCarrick-Walmsley,R., Akerblad,P., Sigvardsson,M. and Kadesch,T. (2003) Inhibition of p300/CBP by early B-cell factor. *Mol. Cell. Biol.*, **23**, 3837–3846.

177. Ito,A., Lai,C.H., Zhao,X., Saito,S., Hamilton,M.H., Appella,E. and Yao,T.P. (2001) p300/CBP-mediated p53 acetylation is commonly induced by p53-activating agents and inhibited by MDM2. *EMBO J.*, **20**, 1331–1340.

178. Kobet,E., Zeng,X., Zhu,Y., Keller,D. and Lu,H. (2000) MDM2 inhibits p300-mediated p53 acetylation and activation by forming a ternary complex with the two proteins. *Proc. Natl Acad. Sci. USA*, **97**, 12547–12552.

179. Jin,Y., Zeng,S.X., Dai,M.S., Yang,X.J. and Lu,H. (2002) MDM2 inhibits PCAF (p300/CREB-binding protein-associated factor)-mediated p53 acetylation. *J. Biol. Chem.*, **27**, 30838–30843.

180. Merienne,K., Pannetier,S., Harel-Bellan,A. and Sassone-Corsi,P. (2001) Mitogen-regulated RSK2-CBP interaction controls their kinase and acetylase activities. *Mol. Cell. Biol.*, **21**, 7089–7096.

181. Ait-Si-Ali,S., Ramirez,S., Barre,F.X., Dkhissi,F., Magnaghi-Jaulin,L., Girault,J.A., Robin,P., Knibiehler,M., Pritchard,L.L., Ducommun,B. *et al.* (1998) Histone acetyltransferase activity of CBP is controlled by cycle-dependent kinases and oncoprotein E1A. *Nature*, **396**, 184–186.

182. Chakravarti,D., Ogryzko,V., Kao,H.Y., Nash,A., Chen,H., Nakatani,Y. and Evans,R.M. (1999) A viral mechanism for inhibition of p300 and PCAF acetyltransferase activity. *Cell*, **96**, 393–403.

183. Liu,Y., Colosimo,A.L., Yang,X.J. and Liao,D. (2000) Adenovirus E1B 55-kilodalton oncoprotein inhibits p53 acetylation by PCAF. *Mol. Cell. Biol.*, **20**, 5540–5553.

184. Valls,E., de la Cruz,X. and Martinez-Balbas,M.A. (2003) The SV40 T antigen modulates CBP histone acetyltransferase activity. *Nucleic Acids Res.*, **31**, 3114–3122.

185. Avvakumov,N., Torchia,J. and Mymryk,J.S. (2003) Interaction of the HPV E7 proteins with the pCAF acetyltransferase. *Oncogene*, **22**, 3833–3841.

186. Col,E., Gilquin,B., Caron,C. and Khochbin,S. (2002) Tat-controlled protein acetylation. *J. Biol. Chem.*, **277**, 37955–37960.

187. Lemercier,C., Legube,G., Caron,C., Louwagie,M., Garin,J., Trouche,D. and Khochbin,S. (2003) Tip60 acetyltransferase activity is controlled by phosphorylation. *J. Biol. Chem.*, **278**, 4713–4718.

188. Poizat,C., Sartorelli,V., Chung,G., Kloner,R.A. and Kedes,L. (2000) Proteasome-mediated degradation of the coactivator p300 impairs cardiac transcription. *Mol. Cell. Biol.*, **20**, 8643–8654.

189. Legube,G., Linares,L.K., Lemercier,C., Scheffner,M., Khochbin,S. and Trouche,D. (2002) Tip60 is targeted to proteasome-mediated degradation by Mdm2 and accumulates after UV irradiation. *EMBO J.*, **21**, 1704–1712.

190. Marambaud,P., Wen,P.H., Dutt,A., Shioi,J., Takashima,A., Siman,R. and Robakis,N.K. (2003) A CBP binding transcriptional repressor produced by the PS1/epsilon-cleavage of N-cadherin is inhibited by PS1 FAD mutations. *Cell*, **114**, 635–645.

191. Girdwood,D., Bumpass,D., Vaughan,O.A., Thain,A., Anderson,L.A., Snowden,A.W., Garcia-Wilson,E., Perkins,N.D. and Hay,R.T. (2003) P300 transcriptional repression is mediated by SUMO modification. *Mol. Cell*, **11**, 1043–1054.

192. Rouaux,C., Jokic,N., Mbebi,C., Boutillier,S., Loeffler,J.P. and Boutillier,A.L. (2003) Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. *EMBO J.*, **22**, 6537–6549.

193. Imhof,A. and Wolffe,A.P. (1999) Purification and properties of the *Xenopus* Hat1 acetyltransferase: association with the 14-3-3 proteins in the oocyte nucleus. *Biochemistry*, **38**, 13085–13093.

194. Lee,H.J., Chun,M. and Kandror,K.V. (2001) Tip60 and HDAC7 interact with the endothelin receptor a and may be involved in downstream signaling. *J. Biol. Chem.*, **276**, 16597–16600.

195. Kleff,S., Andrulis,E.D., Anderson,C.W. and Sternglanz,R. (1995) Identification of a gene encoding a yeast histone H4 acetyltransferase. *J. Biol. Chem.*, **270**, 24674–24677.

196. Verreault,A., Kaufman,P.D., Kobayashi,R. and Stillman,B. (1996) Nucleosome assembly by a complex of CAF-1 and acetylated histones H3/H4. *Cell*, **87**, 95–104.

197. Parthun,M.R., Widom,J. and Gottschling,D.E. (1996) The major cytoplasmic histone acetyltransferase in yeast: links to chromatin replication and histone metabolism. *Cell*, **87**, 85–94.

198. Vogelauer,M., Wu,J., Suka,N. and Grunstein,M. (2000) Global histone acetylation and deacetylation in yeast. *Nature*, **408**, 495–498.

199. Mujtaba,S., He,Y., Zeng,L., Farooq,A., Carlson,J.E., Ott,M., Verdin,E. and Zhou,M.M. (2002) Structural basis of lysine-acetylated HIV-1 Tat recognition by PCAF bromodomain. *Mol. Cell*, **9**, 575–586.

200. Kaehlcke,K., Dorr,A., Hetzer-Egger,C., Kiermer,V., Henklein,P., Schnoelzer,M., Loret,E., Cole,P.A., Verdin,E. and Ott,M. (2003)

Acetylation of Tat defines a cyclinT1-independent step in HIV transactivation. *Mol. Cell*, **12**, 167–176.

201. Bauer,W.R., Hayes,J.J., White,J.H. and Wolffe,A.P. (1994) Nucleosome structural changes due to acetylation. *J. Mol. Biol.*, **236**, 685–690.

202. Garcia-Ramirez,M., Rocchini,C. and Ausio,J. (1995) Modulation of chromatin folding by histone acetylation. *J. Biol. Chem.*, **270**, 17923–17928.

203. Wang,X., He,C., Moore,S.C. and Ausio,J. (2001) Effects of histone acetylation on the solubility and folding of the chromatin fiber. *J. Biol. Chem.*, **276**, 12764–12768.

204. Hansen,J.C. (2002) Conformational dynamics of the chromatin fiber in solution: determinants, mechanisms and functions. *Annu. Rev. Biophys. Biomol. Struct.*, **31**, 361–369.

205. Giandomenico,V., Simonsson,M., Gronroos,E. and Ericsson,J. (2003) Coactivator-dependent acetylation stabilizes members of the SREBP family of transcription factors. *Mol. Cell. Biol.*, **23**, 2587–2599.

206. Shankaranarayana,G.D., Motamedi,M.R., Moazed,D. and Grewal,S.I. (2003) Sir2 regulates histone H3 lysine 9 methylation and heterochromatin assembly in fission yeast. *Curr. Biol.*, **13**, 1240–1246.

207. Grewal,S.I. and Elgin,S.C. (2002) Heterochromatin: new possibilities for the inheritance of structure. *Curr. Opin. Genet. Dev.*, **12**, 178–187.

208. Pawson,T. and Saxton,T.M. (1999) Signaling networks—do all roads lead to the same genes? *Cell*, **97**, 675–678.

209. Yaffe,M.B. (2002) Phosphotyrosine-binding domains in signal transduction. *Nature Rev. Mol. Cell Biol.*, **3**, 177–186.

210. Dhalluin,C., Carlson,J.E., Zeng,L., He,C., Aggarwal,A.K. and Zhou,M.M. (1999) Structure and ligand of a histone acetyltransferase bromodomain. *Nature*, **399**, 491–496.

211. Jacobson,R.H., Ladurner,A.G., King,D.S. and Tjian,R. (2000) Structure and function of a human TAFII250 double bromodomain module. *Science*, **288**, 1422–1425.

212. Hudson,B.P., Martinez-Yamout,M.A., Dyson,H.J. and Wright,P.E. (2000) Solution structure and acetyl-lysine binding activity of the GCN5 bromodomain. *J. Mol. Biol.*, **304**, 355–370.

213. Owen,D.J., Ornaghi,P., Yang,J.C., Lowe,N., Evans,P.R., Ballario,P., Neuhaus,D., Filetici,P. and Travers,A.A. (2000) The structural basis for the recognition of acetylated histone H4 by the bromodomain of histone acetyltransferase Gcn5p. *EMBO J.*, **19**, 6141–6149.

214. Hassan,A.H., Prochasson,P., Neely,K.E., Galasinski,S.C., Chandy,M., Carrozza,M.J. and Workman,J.L. (2002) Function and selectivity of bromodomains in anchoring chromatin-modifying complexes to promoter nucleosomes. *Cell*, **111**, 369–379.

215. Matangkasombut,O. and Buratowski,S. (2003) Different sensitivities of bromodomain factors 1 and 2 to histone H4 acetylation. *Mol. Cell*, **11**, 353–363.

216. Ladurner,A.G., Inouye,C., Jain,R. and Tjian,R. (2003) Bromodomains mediate an acetyl-histone encoded antisilencing function at heterochromatin boundaries. *Mol. Cell*, **11**, 365–376.

217. Zeng,L. and Zhou,M.M. (2002) Bromodomain: an acetyl-lysine binding domain. *FEBS Lett.*, **513**, 124–128.

218. Soutoglou,E., Katrakili,N. and Talianidis,I. (2000) Acetylation regulates transcription factor activity at multiple levels. *Mol. Cell*, **5**, 745–751.

219. Pawson,T. and Nash,P. (2003) Assembly of cell regulatory systems through protein interaction domains. *Science*, **300**, 445–452.

220. Frisch,S.M. and Mymryk,J.S. (2002) Adenovirus-5 E1A: paradox and paradigm. *Nature Rev. Mol. Cell Biol.*, **3**, 441–452.

221. McMahon,S.B., Wood,M.A. and Cole,M.D. (2000) The essential cofactor TRRAP recruits the histone acetyltransferase hGCN5 to c-Myc. *Mol. Cell. Biol.*, **20**, 556–562.

222. Eid,J.E., Kung,A.L., Scully,R. and Livingston,D.M. (2000) p300 interacts with the nuclear proto-oncoprotein SYT as part of the active control of cell adhesion. *Cell*, **102**, 839–848.

223. Halkidou,K., Gnanapragasam,V.J., Mehta,P.B., Logan,I.R., Brady,M.E., Cook,S., Leung,H.Y., Neal,D.E. and Robson,C.N. (2003) Expression of Tip60, an androgen receptor coactivator and its role in prostate cancer development. *Oncogene*, **22**, 2466–2477.

224. Petrij,F., Giles,R.H., Dauwerse,H.G., Saris,J.J., Hennekam,R.C., Masuno,M., Tommerup,N., van Ommen,G.J., Goodman,R.H., Peters,D.J. *et al*. (1995) Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature*, **376**, 348–351.

225. Muraoka,M., Konishi,M., Kikuchi-Yanoshita,R., Tanaka,K., Shitara,N., Chong,J.M., Iwama,T. and Miyaki,M. (1996) p300 gene alterations in colorectal and gastric carcinomas. *Oncogene*, **12**, 1565–1569.

226. Gayther,S.A., Batley,S.J., Linger,L., Bannister,A., Thorpe,K., Chin,S.F., Daigo,Y., Russell,P., Wilson,A., Sowter,H.M. *et al.* (2000) Mutations truncating the EP300 acetylase in human cancers. *Nature Genet.*, **24**, 300–303.

227. Suganuma,T., Kawabata,M., Ohshima,T. and Ikeda,M.A. (2002) Growth suppression of human carcinoma cells by reintroduction of the p300 coactivator. *Proc. Natl Acad. Sci. USA*, **99**, 13073–13078.

228. Yao,T.P., Oh,S.P., Fuchs,M., Zhou,N.D., Ch'ng,L.E., Newsome,D., Bronson,R.T., Li,E., Livingston,D.M. and Eckner,R. (1998) Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. *Cell*, **93**, 361–372.

229. Oike,Y., Takakura,N., Hata,A., Kaname,T., Akizuki,M., Yamaguchi,Y., Yasue,H., Araki,K., Yamamura,K. and Suda,T. (1999) Mice homozygous for a truncated form of CREB-binding protein exhibit defects in hematopoiesis and vasculo-angiogenesis. *Blood*, **93**, 2771–2779.

230. Kung,A.L., Rebel,V.I., Bronson,R.T., Ch'ng,L.E., Sieff,C.A., Livingston,D.M. and Yao,T.P. (2000) Gene dose-dependent control of hematopoiesis and hematologic tumor suppression by CBP. *Genes Dev.*, **14**, 272–277.

231. Rebel,V.I., Kung,A.L., Tanner,E.A., Yang,H., Bronson,R.T. and Livingston,D. (2002) Distinct roles for CREB-binding protein and p300 in hematopoietic stem cell self-renewal. *Proc. Natl Acad. Sci. USA*, **99**, 14789–14794.

232. Sobulo,O.M., Borrow,J., Tomek,R., Reshmi,S., Harden,A., Schlegelberger,B., Housman,D., Doggett,N.A., Rowley,J.D. and Zeleznik-Le,N.J. (1997) MLL is fused to CBP, a histone acetyltransferase, in therapy-related acute myeloid leukemia with a t(11;16)(q23;p13.3). *Proc. Natl Acad. Sci. USA*, **94**, 8732–8737.

233. Rowley,J.D., Reshmi,S., Sobulo,O., Musvee,T., Anastasi,J., Raimondi,S., Schneider,N.R., Barredo,J.C., Cantu,E.S., Schlegelberger,B. *et al.* (1997) All patients with the T(11;16)(q23;p13.3) that involves MLL and CBP have treatment-related hematologic disorders. *Blood*, **90**, 535–541.

234. Ida,K., Kitabayashi,I., Taki,T., Taniwaki,M., Noro,K., Yamamoto,M., Ohki,M. and Hayashi,Y. (1997) Adenoviral E1A-associated protein p300 is involved in acute myeloid leukemia with t(11;22)(q23;q13). *Blood*, **90**, 4699–4704.

235. Taki,T., Sako,M., Tsuchida,M. and Hayashi,Y. (1997) The t(11;16)(q23;p13) translocation in myelodysplastic syndrome fuses the MLL gene to the CBP gene. *Blood*, **89**, 3945–3950.

236. Satake,N., Ishida,Y., Otoh,Y., Hinohara,S., Kobayashi,H., Sakashita,A., Maseki,N. and Kaneko,Y. (1997) Novel MLL-CBP fusion transcript in the therapy-related chronic myelomonocytic leukemia with a t(11;16)(q23;13) chromosome translocation. *Genes Chromosomes Cancer*, **20**, 60–63.

237. Sugita,K., Taki,T., Hayashi,Y., Shimaoka,H., Kumazaki,H., Inoue,H., Konno,Y., Taniwaki,M., Kurosawa,H. and Eguchi,M. (2000) t(11;16)(q23;p13) which developed in an acute lymphoblastic leukemia patient with Fanconi anemia. *Genes Chromosomes Cancer*, **27**, 264–269.

238. Hayashi,Y., Honma,Y., Niitsu,N., Taki,T., Bessho,F., Sako,M., Mori,T., Yanagisawa,M., Tsuji,K. and Nakahata,T. (2000) SN-1, a novel leukemic cell line with t(11;16)(q23;p13): myeloid characteristics and resistance to retinoids and vitamin D3. *Cancer Res.*, **60**, 1139–1145.

239. Panagopoulos,I., Isaksson,M., Lindvall,C., Bjorkholm,M., Ahlgren,T., Fioretos,T., Heim,S., Mitelman,F. and Johansson,B. (2000) RT-PCR analysis of the MOZ-CBP and CBP-MOZ chimeric transcripts in acute myeloid leukemias with t(8;16)(p11;p13). *Genes Chromosomes Cancer*, **28**, 415–424.

240. Chaffanet,M., Gressin,L., Preudhomme,C., Soenen-Cornu,V., Birnbaum,D. and Pebusque,M.J. (2000) MOZ is fused to p300 in an acute monocytic leukemia with t(8;22). *Genes Chromosomes Cancer*, **28**, 138–144.

241. Kitabayashi,I., Aikawa,Y., Yokoyama,A., Hosoda,F., Nagai,M., Kakazu,N., Abe,T. and Ohki,M. (2001) Fusion of MOZ and p300 histone acetyltransferases in acute monocytic leukemia with a t(8;22)(p11;q13) chromosome translocation. *Leukemia*, **15**, 89–94.

242. Carapeti,M., Aguiar,R.C., Goldman,J.M. and Cross,N.C. (1998) A novel fusion between MOZ and the nuclear receptor coactivator TIF2 in acute myeloid leukemia. *Blood*, **91**, 3127–3133.

243. Liang,J., Prouty,L., Williams,B.J., Dayton,M.A. and Blanchard,K.L. (1998) Acute mixed lineage leukemia with an inv(8)(p11q13) resulting in fusion of the genes for MOZ and TIF2. *Blood*, **92**, 2118–2122.

244. Carapeti,M., Aguiar,R.C., Watmore,A.E., Goldman,J.M. and Cross,N.C. (1999) Consistent fusion of MOZ and TIF2 in AML with inv(8)(p11q13). *Cancer Genet. Cytogenet.*, **113**, 70–72.

245. Imamura,T., Kakazu,N., Hibi,S., Morimoto,A., Fukushima,Y., Ijuin,I., Hada,S., Kitabayashi,I., Abe,T. and Imashuku,S. (2003) Rearrangement of the MOZ gene in pediatric therapy-related myelodysplastic syndrome with a novel chromosomal translocation t(2;8)(p23;p11). *Genes Chromosomes Cancer*, **36**, 413–419.

246. Panagopoulos,I., Fioretos,T., Isaksson,M., Samuelsson,U., Billstrom,R., Strombeck,B., Mitelman,F. and Johansson,B. (2001) Fusion of the MORF and CBP genes in acute myeloid leukemia with the t(10;16)(q22;p13). *Hum. Mol. Genet.*, **10**, 395–404.

247. Kojima,K., Kaneda,K., Yoshida,C., Dansako,H., Fujii,N., Yano,T., Shinagawa,K., Yasukawa,M., Fujita,S. and Tanimoto,M. (2003) A novel fusion variant of the MORF and CBP genes detected in therapy-related myelodysplastic syndrome with t(10;16)(q22;p13). *Br. J. Haematol.*, **120**, 271–273.

248. Lavau,C., Du,C., Thirman,M. and Zeleznik-Le,N. (2000) Chromatin-related properties of CBP fused to MLL generate a myelodysplastic syndrome that evolves into myeloid leukemia. *EMBO J.*, **19**, 4655–4664.

249. Hsieh,J.J., Cheng,E.H. and Korsmeyer,S.J. (2003) Taspase1: a threonine aspartase required for cleavage of MLL and proper HOX gene expression. *Cell*, **115**, 293–303.

250. Ayton,P.M. and Cleary,M.L. (2003) Transformation of myeloid progenitors by MLL oncoproteins is dependent on Hoxa7 and Hoxa9. *Genes Dev.*, **17**, 2298–2307.

251. Antonchuk,J., Sauvageau,G. and Humphries,R.K. (2002) HOXB4-induced expansion of adult hematopoietic stem cells *ex vivo*. *Cell*, **109**, 39–45.

252. Xu,W., Edmondson,D.G., Evrard,Y.A., Wakamiya,M., Behringer,R.R. and Roth,S.Y. (2000) Loss of Gcn5l2 leads to increased apoptosis and mesodermal defects during mouse development. *Nature Genet.*, **26**, 229–232.

253. Yamauchi,T., Yamauchi,J., Kuwata,T., Tamura,T., Yamashita,T., Bae,N., Westphal,H., Ozato,K. and Nakatani,Y. (2000) Distinct but overlapping roles of histone acetylase PCAF and of the closely related PCAF-B/GCN5 in mouse embryogenesis. *Proc. Natl Acad. Sci. USA*, **97**, 11303–11306.

254. Haynes,S.R., Dollard,C., Winston,F., Beck,S., Trowsdale,J. and Dawid,I.B. (1992) The bromodomain: a conserved sequence found in human, *Drosophila* and yeast proteins. *Nucleic Acids Res.*, **20**, 2603.

255. Jeanmougin,F., Wurtz,J.M., Le Douarin,B., Chambon,P. and Losson,R. (1997) The bromodomain revisited. *Trends Biochem. Sci.*, **22**, 151–153.

256. Yaffe,M.B., Rittinger,K., Volinia,S., Caron,P.R., Aitken,A., Leffers,H., Gamblin,S.J., Smerdon,S.J. and Cantley,L.C. (1997) The structural basis for 14-3-3:phosphopeptide binding specificity. *Cell*, **91**, 961–971.

257. Steffan,J.S., Bodai,L., Pallos,J., Poelman,M., McCampbell,A., Apostol,B.L., Kazantsev,A., Schmidt,E., Zhu,Y.Z., Greenwald,M. *et al*. (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in *Drosophila*. *Nature*, **413**, 739–743.

258. Nucifora,F.C.J., Sasaki,M., Peters,M.F., Huang,H., Cooper,J.K., Yamada,M., Takahashi,H., Tsuji,S., Troncoso,J., Dawson,V.L. *et al*. (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. *Science*, **291**, 2423–2428.

259. McCampbell,A. and Fischbeck,K.H. (2001) Polyglutamine and CBP: fatal attraction? *Nature Med.*, **7**, 528–530.

260. Hughes,R.E. (2002) Polyglutamine disease: acetyltransferases awry. *Curr. Biol.*, **12**, R141–R143.

261. Marks,P.A., Richon,V.M., Breslow,R. and Rifkind,R.A. (2001) Histone deacetylase inhibitors as new cancer drugs. *Curr. Opin. Oncol.*, **13**, 477–483.

262. Howitz,K.T., Bitterman,K.J., Cohen,H.Y., Lamming,D.W., Lavu,S., Wood,J.G., Zipkin,R.E., Chung,P., Kisielewski,A., Zhang,L.L. *et al*. (2003) Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, **425**, 191–196.

263. Lau,O.D., Kundu,T.K., Soccio,R.E., Ait-Si-Ali,S., Khalil,E.M., Vassilev,A., Wolffe,A.P., Nakatani,Y., Roeder,R.G. and Cole,P.A. (2000) HATs off: selective synthetic inhibitors of the histone acetyltransferases p300 and PCAF. *Mol. Cell*, **5**, 589–595.

264. Balasubramanyam,K., Swaminathan,V., Ranganathan,A. and Kundu,T.K. (2003) Small molecule modulators of histone acetyltransferase p300. *J. Biol. Chem.*, **278**, 19134–19140.

265. Cebrat,M., Kim,C.M., Thompson,P.R., Daugherty,M. and Cole,P.A. (2003) Synthesis and analysis of potential prodrugs of coenzyme A analogues for the inhibition of the histone acetyltransferase p300. *Bioorg. Med. Chem.*, **11**, 3307–3313.

266. Grozinger,C.M., Chao,E.D., Blackwell,H.E., Moazed,D. and Schreiber,S.L. (2001) Identification of a class of small molecule inhibitors of the sirtuin family of NAD-dependent deacetylases by phenotypic screening. *J. Biol. Chem.*, **276**, 38837–38843.

267. Bedalov,A., Gatbonton,T., Irvine,W.P., Gottschling,D.E. and Simon,J.A. (2001) Identification of a small molecule inhibitor of Sir2p. *Proc. Natl Acad. Sci. USA*, **98**, 15113–15318.